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THE POSSIBLE ROLE OF THE GEL-FIBER RATIO OF CONNECTIVE TISSUE IN THE AGING PROCESS*

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IT IS IMPERATIVE to separate the reduced reactivity which we believe to be the essential characteristic of aging from the causes leading to aging. Similarly it is essential to separate the appearances and results of aging from the fundamental processes of aging. These distinctions have often but not always been maintained.

For example, a considerable amount of investigation has been devoted to the question of aging of individual cells of metazoan organisms (2). Much evidence points to certain functional and structural changes within the cell, to a diminished growth capacity of the cell with age of the organism. The point has been argued whether these are primary causes, intrinsic to the cell, or whether they are intracellular events caused by extracellular primary changes. If the latter, are they the causes or results of impaired functional reactivity?

Many observers believe that a cell is essentially immortal in an optimal environment. Child (1) stated that "if we could control the character and amount of nutrition of a cell with sufficient accuracy, it might be possible to keep it physiologically young indefinitely without division." Pearl (6) stated that "the individual cells and tissues of the body in and by themselves are potentially immortal."

The thesis is presented that certain events take place in the connective tissue during growth which ultimately lead to the acceleration of the aging phenomenon. The connective tissue is the milieu through which the cell must ultimately receive its nutrients and by which it maintains its relationship with the remainder of the organism.

An investigation was undertaken of the chemical constitution of the intercellular materials of various tissues and substantial differences were found as the animal grew. The nature of these changes is such that they would cause an increasing impediment to the exchange of nutrients and waste products among the cells.

EXPERIMENTAL

Skin.

In work previously carried out in this laboratory the growth of collagen and the hexosamine-containing material in the skin and femurs of the rat were investigated (9, 10). Hexosamine is a constituent of the mucopolysaccharides of connective tissue which in free form and in combination with protein constitute the ground substance in which the collagen fibers lie. Regression equations were derived which correlate the quantity of these constituents with the weight and size of the animal as measured by femur length for animals up to 250 Gm. in weight.

Table 1 shows the quantity of collagen and hexosamine present in the skin of the rat at each weight level. The deposition rate of each constituent per gram gain in body weight (as derived from the regression equations) is also tabulated. Collagen is deposited at an increasing rate as the animal grows but the deposition rate for hexosamine is almost proportional to the gain in weight. Consequently at each weight range the ratio of hexosamine to collagen decreases as the animal grows. The disproportionate deposition rate of these constitutents continues for at least a year, for

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the hexosamine-collagen ratio (H/C)* continues to fall in these animals also. The implications of these observations are that in the 1 year old rats, a given quantity of collagen is present in the skin, surrounded by less than half the quantity of hexosamine containing gel, than it is in newly weaned rats.† It cannot as yet be said from these data that the decrease in H/C is related to age. Rather the H/C decreases as the size of the animal increases. The male rat continues to grow as it becomes older, but the female rat "plateaus" so that the H/C of a mature female rat is greater than that of a male rat of the same age, but is the same as that of a younger male rat of the same size.

The change in the H/C of the skin was observed in other species. While the total collagen and hexosamine contents were not estimated, the H/C was determined on samples of skin from the guinea pig, squab, rabbit, and human using the technique previously described (10). It may be seen in table 2 that in the guinea pig the H/C decreases in a similar fashion as in the rat skin. As with the rat, it is uncertain whether the decrease in H/C is related to growth or aging.

The squab may be a more satisfactory animal in which to study this phenomenon, because unlike the rat and guinea pig this species ceases to grow shortly after maturity has been attained, as in man. The data in table 3 would seem to indicate that in this species, at least, the H/C does not continue to fall after maximum growth has been attained.

The skin of rabbits was also analyzed (table 4). The H/C values decreased with growth as in the previous instances. In the 3 year old animals the H/C values were somewhat higher than in the 1½ year old animals. However, when the data from these groups were rearranged according to the femur length rather than the stated age, it seemed that the H/C values were inversely related to the femur length. The femur length, in the absence of pathologic distortion, is related to the maximum growth attained by the organism.

*H/C will hereafter refer to the hexosamine-collagen ratio.
†Since collagen can bind the mucopolysaccharides, the discrepancy in the H/C may be even greater (3).

TABLE 1. CONTENTS, DEPOSITION RATES OF COLLAGEN AND HEXOSAMINE, AND H/C OF THE SKIN OF RATS.

Wt. of Rat (Gm.)	Collagen (Mg.)	dH/dw*	Hexosamine (Mg.)	dC/dw*	H/C
50	500	.107	5.0	13.8	.0100
100	1320	.110	10.2	18.3	.0078
150	2340	.112	15.5	21.6	.0067
200	3530	.113	20.9	24.4	.0061
250	4880	.115	26.9	26.6	.0056
300†					.00454
400†					.00437

*Mg. deposited per Gm. of body weight gained, calculated from regression equations (10).
†Obtained from data on 1 year old rats.

TABLE 2. H/C OF THE SKIN AND FEMURS OF GUINEA PIGS.

Age	Wt. (Gm.)	No. of Animals	Skin H/C*	No. of Animals	Femur H/C*
21 days....	125	2	.0125	–	——
36 days....	250	6	.0080	3	.042
90-120 days.	525	4	.0050	4	.029
270 days...	730	2	.0047	2	.015
3½ years...	700	2	.0045	2	.013
Unknown...	1107	1	.0043	–	——

*Mean values.

TABLE 3. H/C OF THE SKIN OF SQUABS.

Age	Number	Femur Length (Cm.)*	H/C*
2½ weeks.....	2	4.22	.0183
4 weeks.....	2	4.33	.0160
10 months.....	4	4.50	.0130
4-6 years.....	4	4.64	.0131

*Mean values.

The results of analyses of human skin were of considerable interest. Pieces of abdominal skin were obtained at autopsy. The H/C

TABLE 4. H/C OF THE SKIN OF RABBITS.

GROUP A		Age of Animals	GROUP B	
Mean Femur Length (Cm.)	Mean H/C		Mean Femur Length (Cm.)	Mean H/C
7.40	.0106	8-10 weeks	7.43	.0150
8.50	.0096	4-6 months	8.29	.0080
9.56	.0073	1½ years	9.65	.0061
9.55	.0079	3 years	9.51	.0071
9.27	.0098	1½-3 years	9.42	.0075
9.85	.0052	1½-3 years	9.74	.0057

The rabbits of Group A and Group B were from different sources. Each value represents the mean of data obtained on 4 animals. The data obtained from 1½ year and 3 year old rabbits were pooled and redistributed according to the growth attained as measured by femur length.

TABLE 5. H/C OF SKIN FROM HUMANS TAKEN AT AUTOPSY.

Age	Number	H/C*
1 month	14	.0096± .0016†
1 month–1 year	12	.0079± .0017
1 year–12 years	12	.0070± .0015
40 years–75 years	9 men "acute" death	.0055± .0017
	7 men "chronic" death	.0040± .0004
	16 men (total)	.0048± .0009
	5 women "acute" death	.0050± .0015
	6 women "chronic" death	.0037± .0003
	11 women (total)	.0043± .0012

*Mean value.
†Standard deviation.

values of the skin of individuals above 40 years of age were approximately one half that of the newborn (table 5). There were no significant sex differences. Among the adults there was no relationship between the height and the H/C.

Femurs.

In a previous communication it was reported that the collagen and hexosamine content of the femurs of the rat were investigated (9). In table 6 the contents of these constituents in the femurs at different weight

TABLE 6. CONTENTS, DEPOSITION RATES OF COLLAGEN AND HEXOSAMINE AND H/C OF THE FEMURS OF RATS.

Wt. of Rat (Gm.)	Collagen (Mg.)	dC/dw*	Hexosamine (Mg.)	dH/dw*	H/C
50	32.78	.591	1.438	.0134	.0437
100	61.45	.554	1.987	.00926	.0319
150	88.80	.534	2.399	.00746	.0266
200	115.70	.521	2.747	.00641	.0233
250	141.40	.509	3.043	.00568	.0212
300†					.0197
400†					.0187

*Mg. deposited per Gm. of body weight gained, calculated from regression equations (9).
†Obtained from data on 1 year old rats.

TABLE 7. H/C AND H/F OF LUNG TISSUE FROM RABBITS.

	H/C	H/F*	C/F
8-10 weeks	.2141	.0807	.37
4-6 months	.1315	.0554	.41
1½ years	.1286	.0473	.37
3 years	.1040	.0372	.36

*F = total fibrillar protein, i.e., collagen plus elastin. Collagen and elastin were determined by the method of Neuman and Logan (5). Each value represents the mean data obtained on 4 animals.

levels are shown. The rate of deposition differs from that in the skin. Collagen is deposited at a slightly decreasing rate during growth. The rate of deposition of the hexosamine containing material decreases quite markedly. This results in a similar decrease in H/C during growth, as in the skin. The H/C continues to fall in one year old rats.

In table 2 similar data are shown for the guinea pig.

Lung.

In the skin and femur, collagen is by far the most important fibrillar constituent of the connective tissue. The elastin content is low. In certain other tissues, elastin constitutes the major fibrillar protein. The collagen, elastin,

and hexosamine relationships were determined in portions of the lower lung of rabbits. It was observed that both the H/C and H/F* decrease with age (table 7). Unlike the skin and femurs, the decrease in the ratios correlates with age rather than with femur length. Since the ratio of collagen to total fiber is constant it would appear that both collagen and elastin are deposited at the same rate.

Effect of Cortisone Administration.

In a previous communication, the results of an investigation of the effect of cortisone on the hexosamine and collagen content of the skin and femurs were reported (8). It was observed that even though large losses in weight occurred there was little, if any, loss of collagen from these organs. However, there was a considerable diminution of the hexosamine-containing material. This would obviously cause a fall in H/C. Thus in one year old rats the H/C is approximately .00450 — .00430 for the skin and .0180 — .0190 for the femur. After the administration of cortisone the H/C was reduced to as low as .00355 and .0150, respectively. Similar observations have now been made in rats in other age groups. In this respect it is of considerable interest that human adults who died from "chronic" causes (such as cancer, cirrhosis, etc.) had a lower skin H/C than those who died from relatively acute situations such as myocardial infarction (See table 5).

It has now been determined that following the discontinuation of the cortisone treatment in the rat the H/C reestablishes itself when the animal returns to the original weight.

DISCUSSION

The experimental data presented herein are of limited scope but if they reflect the general situation relative to the connective tissue throughout the whole organism, the following conclusions would seem to be valid.

1. Collagen (and possibly elastin) is deposited in the connective tissue during growth at a faster rate than the hexosamine-containing material which constitutes the gel in which the fibers lie.

2. In the presence of a severe catabolic situation induced by cortisone, collagen is relatively unaffected, but the hexosamine-containing material is considerably diminished.

What bearing have these facts on the problems of aging? The following considerations indicate that the sequence of events which follow the progression of these phenomena in connective tissue may profoundly influence and indeed condition the aging of the cell.

All cells with the possible exception of those floating free in the blood stream are dependent for their survival on the connective tissues which surround them. It is by the way of the blood vessels, capillary walls, membranes, and extracellular fluids that the cell must receive its nourishment at an adequate rate. It is through these systems that the products of metabolism must be removed as well.

While the composition of the connective tissue elements varies considerably, quantitatively, and in some instances qualitatively, the general structure is that of fibrillar components lying within a ground substance gel. The cell then is dependent on the properties of this gel and any alteration taking place within this milieu whether chemical or physical in nature could profoundly influence the nutrition and metabolism of the cell. One such alteration is suggested by the experimental work which has been presented here.

Hexosamine is a constituent of the mucopolysaccharides of connective tissue. In free form and combined with proteins, they produce the gel-like properties of the ground substance. At this time it can be stated that during growth, collagen is deposited at a faster rate than hexosamine, i.e., the ratio of gel to fiber diminishes. Studies are now being carried out to learn if the observations made on the materials described above apply to the organism in respect to age, independently of growth. It would seem that age and growth are related. There is ample experimental data which suggest that the slower the rate of growth of the animal the longer is its life expectancy (4).

During growth then, the cell is dependent on its environment of connective tissue which contains more and more fibers relative to gel. Cowdry (2) states that "the fibers may obstruct the flow of fluid when they are densely matted together." The movement of partic-

*H/F = hexosamine — total fibrillar ratio, i.e., the collagen plus the elastin.

ulate as well as soluble substances through this milieu would become more and more impaired. Thus the natural consequences of growth lead ultimately to a situation which is less and less tenable for the maintenance of adequate nutrition and metabolism of the cell.

This is, indeed, demonstrated by the experiments relative to growth and longevity cited above. The smaller animal has a greater hexosamine/collagen ratio than its larger litter mate. The female rat is considerably smaller than her brother especially as age advances, so that at all times her gel-fiber ratio is greater. The female rat outlives the male rat by a considerable period (4). The difference in longevity in this species is not directly related to sex, but to maximum growth attained by the animal.

Until now the discussion has been related to the alteration in the relative quantities of fiber and gel during the deposition of these materials. Other facts must now be brought into consideration. Once collagen is deposited it is relatively inert metabolically. The hexosamine-containing material is metabolically active, however, and it can be partially removed under the influence of large amounts of cortisone. This is not necessarily a specific effect, however. Any circumstance which would cause a decrease in hexosamine-containing material would decrease the gel-fiber ratio and would enhance the processes relating to aging and age associated conditions. This consideration takes on practical significance for it is well documented that with aging the excretion of urinary corticoids is relatively undiminished but in men and women the excretion of ketosteroids and androgens is diminished (7). These observations could mean that as senescence progresses the secretion of hormones by the adrenal cortex similates more and more a "cortisone-like" action. Thus senescence begets senescence and gel-fiber ratio is progressively diminished.

On the basis of the above discussion, studies are under way to learn if the H/C ratio might be a measure of the "biochemical age" of the individual. Furthermore the influence of certain anabolic agents such as insulin, growth hormone, and androgens on the animal whose H/C ratio has been reduced by cortisone is under investigation.

Only the total hexosamine content of these tissues has been investigated and discussed. Certainly other changes taking place in connective tissue must be considered, such as any alteration which may take place in the composition of the mucopolysaccharides, their water binding capacities, viscosity, and electrostatic charge.

The thesis herein presented points out the role of the connective tissue in the aging process and offers a working hypothesis from which subsequent investigation may proceed.

SUMMARY

Experimental data are presented for the skin, femurs, and lungs which demonstrate that during growth, the fibrillar elements of the connective tissue are deposited at a faster rate than the gel in which these fibrils lie. The quantity of gel can be diminished under the influence of large amounts of cortisone while the deposited collagen seems to be relatively stable. On the basis of these considerations a hypothesis is proposed, namely that aging may be conditioned by the quantity of gel relative to the quantity of fiber in the connective tissue. It is by way of the connective tissue that the cells receive their nutrients and the products of metabolism are removed. As the relative increase in the quantity of fiber occurs there is an impairment in the transfer of these materials and the situation becomes less and less tenable for the maintenance of adequate nutrition and metabolism of the cell.

We wish to acknowledge with thanks the technical assistance of Hilda Lanman. We wish also to thank Dr. Ann Peterson for some of the analytic data.

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YOUNG RATS WITH ADULT ADRENAL TRANSPLANTS: A PHYSIOLOGIC STUDY*

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AGING, EVEN within one species, presents a vague and indeterminate picture. The mass of data which is available on the bodily and mental changes found in aged individuals does not arrange itself into a clear-cut pattern. The number of bodily changes with advancing age which are reasonably constant and which come legitimately under the heading of aging and not under that of maturation, are few. They are, moreover, so trivial that they do nothing to explain the inevitable fall in survival value which overtakes the aging mammal.

It is probable that the sum-total of unfavorable changes which are found in an aged individual is made up by two components, intrinsic deterioration, i.e., aging, and extrinsically acting, deleterious environmental changes, i.e., disease, which overlays and modifies the process of aging. Moreover, aging may be a multicentric phenomenon, acting in different tissues at different times and in different ways with differing intensity. Taken in conjunction, these two suppositions, although by no means exhausting the number of probable variables, would help to explain the extreme variability with which the aging process prints its stamp on the individual. To arrive at a useful understanding of this complex maze of interactions the experimental approach must be analytic. We must endeavor to investigate the changes of aging, tissue by tissue, organ by organ, and function by function. When we try to do this we run into great difficulties of method.

As an example, we might wish to investigate the response of the aged pituitary gland to the epinephrine stimulus as was done by Solomon and Shock (10). We might find, as observed by these authors, that the response to a given dose in terms of adrenocortical reaction was smaller in old than in young individuals. If we let matters rest here we have a valid and valuable piece of information about the functional state of an aged individual; if, however, we want to localize this change exactly we shall have to eliminate any age changes in the mechanisms mediating between the injection of epinephrine and the pituitary gland, such as the rate of absorption and of destruction of epinephrine, the presence of inhibiting substances, and the integrity of pathways as well as any age changes in the mechanisms intervening between the pituitary and the adrenal and between the adrenal and the locus of measurement. At the conclusion of this series of varied and difficult investigations we might be enabled to state that the sensitivity of the pituitary gland to epinephrine stimulation decreases with age but we would still not know whether this was a primary alteration due to intrinsic aging of pituitary tissue or secondary to the aging of one or more of the tissues and organs and functions outside the pituitary on which the gland may depend.

No method of experimentation on the intact animal which is at present practicable can possibly provide an answer to this question. Valuable as they are, both from a descriptive point of view and also as possible starting points for therapeutic action, such experiments shed no light on the *mechanisms* of aging because it is impossible to provide scientifically acceptable controls for this type of experiment. When measuring a function in an aged animal the correct control is thought to be a young animal. This is, however, an erroneous concept. Age is not the only thing which varies between a young and an old individual; they are also separated by a long and usually uncontrollable series of extraneous events which have left their distinctive mark on the aged individual. Secondly, the old animal has not only an older pituitary gland but the entire animal and its functions are also older. Such an experiment cannot therefore be conceived only as the comparison between their pituitary reactions. All these difficulties would resolve themselves if we could compare a young animal with a young hypophysis with another young animal with an old hypophysis and contrast the results with those obtained

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by comparing the reactions of an old animal with an old hypophysis with those of an old animal with a young hypophysis. Changes consistently found in such experiments would have to be accepted as being due to the age (or youth) of the gland and not to any extraneous factor. While it is impossible to apply these principles to the native organs of an animal, they can be applied to transplants. The principles and limitations of this method of investigating aging mechanisms have been outlined elsewhere (5,6), but it must be emphasized that this is at present the only experimental approach which can give relevant and exact information on the aging processes of higher organisms. If gerontology up to date is a mass of clever hypotheses and confused data instead of an orderly, expanding discipline within the framework of modern biology, this is entirely due to the lack of experiments using the method of homotransplantation.

In a previous paper an indication was given how the method of homotransplantation might be used to define exactly the role which the adrenal cortex plays in the aging processes of the albino rat (6). The present paper reports further experiments in this field using different age groupings and different function tests and thus enlarging very slightly the negligible amount of knowledge which we so far possess on these matters.

The present study was undertaken to investigate the effect in young rats of replacing their adrenals with adrenocortical transplants from older animals. The functions assessed were growth, reproductive performance, lactation, water diuresis, uropepsin excretion, and potassium tolerance.

EXPERIMENTAL

The animals were Wistar albino rats of the Glaxo strain, a highly inbred strain, and adrenal homotransplantation between its members succeeds in the majority of cases. Ten litters, comprising 57 animals, were used in the main experiment. In addition, breeding experiments were performed on 12 older adrenalectomized females bearing adrenocortical homotransplants.

The animals were divided into normal controls, coeval transplants, and old transplants, and treated as follows:

Normal controls.—These animals, littermates of the two experimental groups, were left intact. They were kept in the same cage as the experimental animals and were subjected at the same time to the same tests. There were 2 males and 10 females in this group.

Coeval transplants.—At the age of 40 days this group underwent bilateral adrenalectomy followed by the insertion of the adrenal capsule of a littermate of the same sex under the left renal capsule. The animals were kept on saline for 10 days following the operation. At the age of 55 days they were mated with normal males. They were left with their litters until 21 days after parturition. At the age of 147 days they were subjected to a water load test and at the age of 182 days to a test of potassium tolerance. The survivors of this test were killed.

There were 7 males and 18 females in this group originally. The transplant failed in 3 females and in 3 males, leaving 4 males and 15 females. After the conclusion of the experiment it was found that adrenalectomy had been incomplete in 1 female. She was therefore excluded from the final analysis, leaving 4 males and 14 females in this group.

Old transplants.—The animals in this group, being littermates of the preceding, were subjected to exactly the same procedures as the coeval transplants and were throughout the test kept together with their normal and coeval controls. The only difference was in the age of the transplanted adrenals, which were from 229 to 373 days older than their hosts and were derived from older animals of the same strain. The average age of the transplanted adrenal at the time of operation was 320 days as compared with 40 days which was the age of the hosts at that time. This group numbered originally 6 males and 14 females. Transplantation failed in 3 males and in 1 female, leaving 3 males and 13 females.

Each animal was examined after death to verify transplant growth, completeness of adrenalectomy, and absence of accessory adrenocortical tissue. Only those animals in which these three criteria were satisfied were used for the final analyses. In addition, blocks of tissue were taken from the gonads, thymus, heart, liver, kidney, skeletal muscle, and skin. The results of these histologic studies will be reported later.

RESULTS

Growth.—All animals were weighed daily for 100 days after the operation, i.e., up to an age of 140 days. In the case of the females the weighing was interrupted as soon as it was obvoius that an animal was pregnant; it was resumed after the litter had been weaned at the age of 3 weeks. There is therefore a gap in the female weight records. Feeding of all animals was identical and ad libidum with a standard cube diet. Figures 1 and 2 show the weight records of the male and female animals, respectively. In both sexes the weight curves for all 3 groups agree closely although in both cases there is a slightly larger increase among the experimental animals and especially among the old transplants. The agreement, although not as close, is more remarkable among the females since they had passed through pregnancy and lactation (which represented a different experience for each individual).

Reproduction.—A. Males.—Two males, one bearing a coeval and the other a transplant 395 days older than the animal itself, were mated on two occasions with 4 normal females each. Table 1 shows that their reproductive performance was normal and that there was no difference between the 2 animals in this respect. Weaning data are omitted as they would mainly reflect the lactational ability of their normal female mates.

B. Females.—At the age of 55 days all females were mated with normal males. As soon as pregnancy was established they were isolated. The litters were counted and the sex recorded at birth and again at 3 weeks when they were also weighed. The mothers were then returned to the experiment. Table 2 shows a summary of the values obtained in these observations. All animals of all 3 groups produced litters within 46 days of mating and there is no significant difference in the time which elapsed before conception. The litter size at birth was identical in coeval and old transplants and slightly larger in the normal controls. On the other hand, survival to weaning age was slightly better in the experimental groups.

Lactational performance, judged by the weight reached by the offspring during the suckling period, was highest among the old transplants and lowest among the normal controls. From table 1 and figure 3 it can be seen that this was not due to the differences in total numbers of offspring or to uneven distribution of litter sizes.

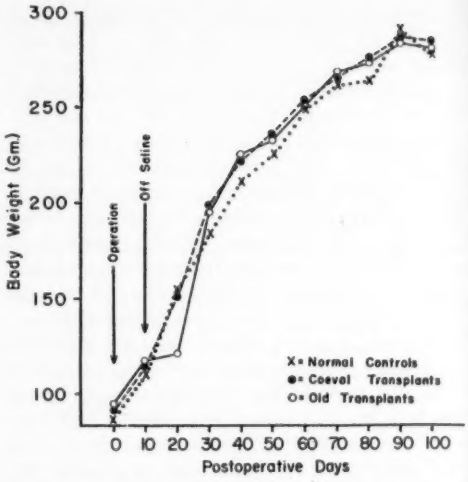

FIG. 1. Growth by weight of male albino rats from the age of 40 to 140 days (operation performed at age of 40 days).

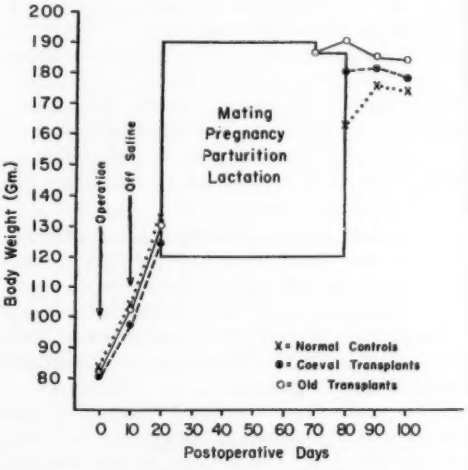

FIG. 2. Growth by weight of female albino rats from the age of 40 to 140 days (operation performed at age of 40 days). Between the ages of 60 and 140 days each animal passed through pregnancy, parturition, and lactation. The slightly increased growth among the transplant bearing animals may be an expression of mild adrenal deficiency.

TABLE 1. REPRODUCTIVE PERFORMANCE OF MALE ADRENALECTOMIZED ALBINO RATS WITH ADRENOCORTICAL TRANSPLANTS.

		Coeval Transplants	Old Transplants
No. of animals		1	1
No. of matings		8	8
No. of litters		7	8
Interval from mating to parturition	Range	24–41 days	26–50 days
	Average	32.1 days	33 days
Size of litters at birth (incl. stillbirths)	Range	4–11	3–12
	Average	8.1	7.5
No. of stillbirths per litter		0.0	0.12
Sex ratio at birth (Male/female)		0.96	0.96

In this series two obstetric mishaps occurred; one death from obstructed labor in the normal controls and one inversion of uterus, followed by failure of lactation and death of the litter, in the old transplants. Such cases occur not infrequently in this colony and have probably no special bearing on the problem under investigation.

A group of 12 females, 100-135 days old and bearing adrenocortical transplants aged 294-805 days, was also mated with normal males. This group had only 3 normal controls and some of the litters were used for other experiments before reaching weaning age. Table 3 shows, however, that full reproductive performance was obtained from females bearing adrenocortical transplants between 294 and 805 days old, i.e., well beyond the normal reproductive period of the albino rat.

TABLE 2. REPRODUCTIVE PERFORMANCE OF FEMALE ADRENALECTOMIZED ALBINO RATS WITH ADRENOCORTICAL TRANSPLANTS.

		Normal Controls	Coeval Transplants	Old Transplants
No. of animals		10	14	13
No. of matings		10 (1 per animal)	14 (1 per animal)	13 (1 per animal)
No. of litters		10	14	13
Interval from mating to parturition	Range	23–43 days	23–46 days	25–42 days
	Average	29.8 days	32.6 days	31.9 days
Size of litters at birth (incl. stillbirths)	Range	4–11	4–11	3–11
	Average	9.1	8.5	8.4
No. of stillbirths per litter		1.70	0.28	0.61
Size of litters at weaning (i.e., 23 days)	Range	0–11	0–11	0–10
	Average	6.6	6.8	7.77
Sex ratio at birth (Male/female)		1.16	0.77	1.11
Average weights at weaning	Per live born	19.7 Gm.	20.7 Gm.	24.7 Gm.
	Per individual weaned	23.5 Gm.	25.2 Gm.	27.4 Gm.
	Modus	24.5 Gm.	27.5 Gm.	28.0 Gm.

Analysis of the first litters of female albino rats. Age at mating, 55 days; average age at parturition, 86 days; average age of old transplant at parturition, 366 days.

TABLE 3. REPRODUCTIVE PERFORMANCE OF 12 ADRENALECTOMIZED FEMALE ALBINO RATS 100-135 DAYS OLD WITH ADRENOCORTICAL TRANSPLANTS AGED 294-805 DAYS.

Age in Days at Mating:		Interval Between Mating and Parturition (Days)	Litter Size and Sex at Birth		No. of Still-births	Litter Size at Weaning	Average Weaning Weights (Gm.)		Remarks
of Mother	of Trans-plant		M	F			Per Live Born	Per Rat Weaned	
105	805	30	5	2	0	—	—	—	Litter used for experiment
105	805	28	3	5	0	8	21.25	21.25	
100	788	24	2	5	0	7	21.0	21.0	
100	403	33	4	5	0	0	—	—	Cannibalism
100	403	26	7	3	0	0	—	—	Cannibalism
100	403	28	2	9	0	10	22.1	24.4	
100	403	28	4	7	0	0	—	—	Cannibalism
135	384	26	5	6	0	11	29.0	29.0	
135	384	24	5	4	0	9	30.7	30.7	
135	384	23	7	4	1	0	—	—	Postpartum death
105	293	33	5	6	0	8	17.7	24.3	
105	293	23	8	2	0	—	—	—	Litter used for experiment

Analysis of the first litters of adrenalectomized female albino rats bearing adrenocortical transplants of various ages. Cannibalism occurring in 3 littermates is probably unrelated to the age of the transplants.

Water load test.—At the age of 147 days each female was given 5 ml. water by stomach tube and its urine was collected for the next 6 hours. This test was repeated on 3 successive days. Figure 4 shows the close agreement of the results, especially up to the point of 50 per cent elimination, indicating that there was no difference among the 3 groups in their ability promptly to eliminate a moderate water load. There were not enough males to make the compilation of their responses worth while.

Uropepsin excretion.—The urines collected during and after the water load tests were assayed for uropepsin according to the method of Fawcett (3). Table 4 shows the results. The concentrations of uropepsin are very similar in the 3 groups, the higher average value in the coeval transplants depending on one

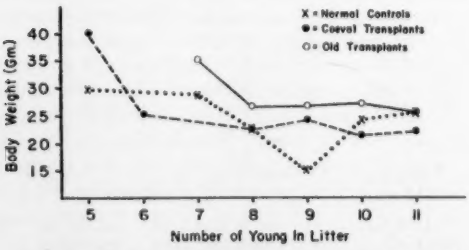

FIG. 3. Weaning weights (at 3 weeks) of first litters of female albino rats according to litter size, showing virtual identity of the 3 groups.

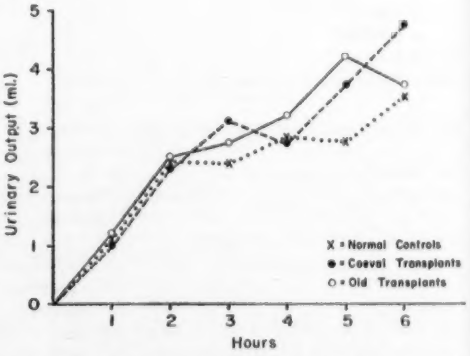

FIG. 4. Rate of renal elimination of a 5 ml. gastric waterload in female albino rats.

single very high result. The rate of excretion per rat is the same in the 2 groups of adrenalectomized animals, regardless of the age of the transplant. The normal controls have a lower rate of excretion (about 30 per cent per rat). This difference persists, although somewhat smaller, (about 20 per cent) when the results are expressed in terms of body weight. It seems therefore that the main reason for the lower excretion of uropepsin

TABLE 4. UROPEPSIN EXCRETION OF 147 DAY OLD FEMALE ALBINO RATS.

No. of Experiment	Test No.	No. of Animals	Average Body Weights (Gm.)	Rat Units* Uropepsin/ Ml. Urine	Rat Units* Uropepsin/ Hour/Rat
			Normal Controls		
I	1	2	173.0	5.0	2.3
	2	2	173.0	4.0	1.1
	3	1	181.0	8.5	1.5
II	1	1	172.0	5.0	3.75
	2	1	172.0	3.75	4.28
	3	1	172.0	6.0	3.3
III	1	4	171.2	5.0	3.4
	2	4	171.2	4.5	1.8
	3	3	179.6	6.0	0.93
IV	1	2	183.5	6.0	1.3
	2	2	183.5	7.0	0.9
	3	2	183.5	6.5	2.3
	Total	25	av. 176.3	av. 5.6	av. 2.23
			Coeval Transplants		
I	1	4	185.2	5.0	4.0
	2	2	189.5	5.0	4.3
	3	2	189.5	6.0	1.44
II	1	1	186.0	5.0	5.0
	2	1	186.0	6.5	4.3
	3	1	186.0	6.0	2.0
III	1	4	187.5	5.5	3.9
	2	4	187.5	5.5	1.8
	3	4	187.5	6.0	3.8
IV	1	3	160.6	7.5	6.6
	2	2	187.0	6.0	0.39
	3	2	187.0	13.5	2.3
	Total	30	av. 193.2	av. 6.46	av. 3.31

TABLE 4. UROPEPSIN EXCRETION OF 147 DAY OLD FEMALE ALBINO RATS—Continued.

No. of Experiment	Test No.	No. of Animals	Average Body Weights (Gm.)	Rat Units* Uropepsin/ Ml. Urine	Rat Units* Uropepsin/ Hour/Rat
			Old Transplants		
I	1	4	191.7	6.0	5.06
	2	4	191.7	5.5	1.42
	3	3	194.3	5.25	3.6
II	1	2	186.5	5.5	5.0
	2	2	186.5	4.5	3.4
	3	1	193.0	6.5	4.33
III	1	5	177.8	6.5	2.6
	2	5	177.8	3.5	2.1
	3	4	185.7	8.0	5.3
IV	1	1	202.0	7.0	1.2
	2	1	202.0	5.0	0.86
	3	1	202.0	6.5	3.8
	Total	33	av. 190.9	av. 5.81	av. 3.22

*10 rat units = 1 Mirsky unit = amount which releases 1 mg. tyrosine in 10 minutes of standard assay.

among the normal controls was a lower urinary output during the test period.

There were not enough male animals to make the compilation of their uropepsin values worth while.

Potassium tolerance.—At the age of 182 days 33 animals were injected intra-peritoneally with a 10 per cent aqueous solution of potassium chloride. The dose was 0.5 mg. per 100 Gm. body weight. The test was repeated on the survivors on the following day. Table 5 shows that there was a highly significant difference between the normal controls, none of which died, and the experimental animals, half of which succumbed. The difference between the old and coeval groups is less striking and there are not enough readings to show whether this difference is a real one.

DISCUSSION

In these experiments two comparisons had to be made; the first between normal controls and adrenalectomized animals bearing transplants, and the second between animals bearing coeval transplants and those with old transplants. The values obtained for the normal controls throw no light on the aging of the adrenal cortex and merely serve to indicate how far transplant function can be equated with normal organ function. The results show that there was no significant difference in the rate of growth, reproductive performance, or in the renal elimination of a moderate water load between normal controls and transplant-bearing animals. On the other hand, both uropepsin excretion and potassium tolerance showed such a difference. This serves to remind us that in experiments of this type we are determining the age changes of transplanted tissues and not of normal organs.

Differences between a normal rat and an adrenalectomized one bearing an adrenocortical transplant, as far as they are known, consist in (a) the absence of an adrenal medulla in the transplant-bearing animals, (b) a slightly diminished total amount of cortical tissue, at any rate where there is only one

TABLE 5. POTASSIUM TOLERANCE OF ADRENALECTOMIZED ALBINO RATS WITH ADRENOCORTICAL TRANSPLANTS.

10% KCl Injected Intraperitoneally at a Dose of 0.5 mg. KCl/100 Gm. Body Weight		Normal Controls	Coeval Transplants	Old Transplants
Males				
Test No. 1	No. of animals	2	3	3
	No. of deaths	0	2	1
Test No. 2	No. of animals	2	1	2
	No. of deaths	0	0	0
Total deaths		0	50%	20%
Females				
Test No. 1	No. of animals	7	9	9
	No. of deaths	0	5	6
Test No. 2	No. of animals	7	4	3
	No. of deaths	0	1	2
Total deaths		0	46%	66%
No. and % of deaths, male and female		0/18 = 0%	8/17 = 47%	9/17 = 53%

transplant, and (c) an atypical position of, and blood supply to, the transplant. To the extent to which these differences can be removed transplants will become more strictly comparable to the normal gland. Meanwhile, the results of the present investigation confirm previous findings (7, 8, 14) that adrenalectomized rats with adrenocortical transplants live in a state of slight adrenal deficiency. This is evidenced by the slightly diminished rate of growth among the normal controls of both sexes and, to an even greater extent, by their higher tolerance to toxic doses of potassium chloride.

The comparison between the two transplant-bearing groups of animals is probably best discussed separately according to functions tested.

Growth.—In both groups growth proceeded at the same normal rate. If there was any significance in the slight differences found, it could only be brought out by further experiments involving much larger numbers of animals.

The period of growth tested (from 40 to 140 days) is a critical one in the albino rat. During this period occurs the fairly sudden slowdown from the prepubertal to the postpubertal rate of growth (1). This change occurred in a normal manner among the animals bearing adult adrenal transplants, which seems to be strong evidence against a primary involvement of the adrenal gland in the mechanism which brings about this slowdown. It has previously been shown that adrenalectomized adult female rats bearing newborn adrenocortical transplants grow for 10 weeks at an accelerated rate (6). These two findings taken in conjunction support the hypothesis that the prepubertal adrenal gland is unable to support normal ovarian activity; but only experiments involving gonadectomized animals can settle this question.

Once the adult growth rate is attained it remains constant for each sex well beyond the age of 420 days. It might therefore be thought that the present investigation merely demonstrates what is already known but this is not the case. The steady adult growth rate could

be the result of the simultaneous increase or decrease of growth-promoting and growth-inhibiting functions. Such a possibility cannot be excluded until the functions in question have been studied in isolation, i.e., after transplantation.

While any difference in the rate of growth between the 2 groups of transplant-bearing animals would have been strong presumptive evidence for an intrinsic age change of adrenocortical tissue, the absence of such a difference cannot be accepted as evidence for the absence of such an age change. It is possible that any intrinsic age change of that nature may have been compensated for by the homeostatic mechanisms of the host, e.g., by increased transplant stimulation through greater output of ACTH. This deadlock can, however, be broken by further suitably designed transplantation experiments. One obvious way would be to extend observation over a longer period.

Reproduction.—There was no marked difference between the reproductive performance of rats bearing coeval transplants and those with old transplants. The reproductive performance of the healthy normal female albino rat does not decline until about the age of 18 months but it was thought justifiable to test transplants of an average of 335 days at the time of mating for reasons stated above. However, a second group, with transplants between 293 and 805 days old, was also investigated and showed normal reproductive records. It seems therefore that female adrenocortical transplants 55 to 805 days old (at the time of mating) are capable of supporting the normal reproductive performance of 55 to 135 days old females; always with the proviso that this may be brought about through the mediation of a compensating mechanism on the part of the host.

The donors for some of the old transplants were multiparous females. The possibility must therefore be considered that their adrenal tissue may have been "primed" for efficient reaction during pregnancy and lactation. This opens up a new line of inquiry about which nothing is known.

Lactation.—This function is treated separately because claims have been advanced that the adrenal cortex plays a specific part in the performance of lactation (9,12). Judged by the weaning weights the age of the transplant had no influence on lactational performance.

Water load test.—The inability of hypoadrenal animals to deal efficiently with a water load is the basis for this adrenal function test. The inability involves probably not only the function of the renal tubules but also the absorption of water from the intestines and its shift from the tissues to the circulation (4). In this investigation, normal disposal of a gastric water load was observed in female adrenalectomized rats 147 days old irrespective of whether they were bearing cortical transplants of the same age of 280 days older (427 days).

Uropepsin excretion.—It has been shown recently that the excretion of pepsinogen into the urine is linked to adrenocortical activity (2,11,13) and we have demonstrated in this laboratory that adrenalectomy in the rat is followed by disappearance of uropepsin. It was therefore thought of interest to measure the levels of uropepsin excretion in the 3 groups of animals. Again, the results in the coeval transplants and the old transplants were practically identical, showing that an age difference between adrenal transplants of 147 days and adrenal transplants of 427 days cannot be demonstrated by these means.

The normal controls showed a significantly lower uropepsin excretion. The reason for this is obscure. It is tempting to suspect that the placement of an adrenal transplant within the substance of the kidney may lead to enhanced tubular excretion of water but one has still to account for the fact that in spite of increased diuresis in the experimental groups the concentration of uropepsin was identical with that in the normal controls.

Potassium tolerance.—This test demonstrated clearly that a stress calling upon the whole corticoid reserves of a rat finds those with one transplant instead of two normal glands at a grave disadvantage. It failed, however, within the limits of the experiment, to produce convincing evidence that an age difference of 280 days between the transplants further impairs the ability of the animal to withstand this biochemical upset. Additional experiments with older transplants and more animals are indicated.

In the absence of a body of knowledge about aging processes, we must accept the findings of this investigation such as they are

without attempting to draw any further conclusions from them. If differences had been discovered in the behavior of the two transplant groups we could have been less cautious but the exact interpretation of negative results must remain uncertain until collateral evidence becomes available.

This investigation suffers from two great defects. The first of these is the insufficient number of animals. The efficient application of the method of homotransplantation to gerontologic problems requires a supply of large numbers of compatible aged donors. To achieve this one would need specialized colonies in which an artificial abolition of the population pyramid is combined with the maximum amount of inbreeding. Intrinsic age changes of various tissues are in all probability quantitatively small and cannot therefore be readily detected unless large numbers of animals are used.

The second defect of this investigation is the limited period of observation. Ideally, any experiment of this sort should be followed up into the old age of the host animals. Age differences which make their appearance at a later stage, either through further aging of the transplant or through the breakdown of compensating mechanisms, could thus be revealed.

One must resist the temptation to correlate these few facts with the great factual literature which already exists on the normal life history of the rat, on adrenal secretions in various age groups in man, and on stress response in old age. Only when patient extension of the transplantation method to other tissues, other animals, and other age groups has provided us with a basis of understanding shall we be able to take profitable note of the facts elucidated by the study of intact animals. Studies on intact animals are building up an increasingly more accurate picture of the results of aging; they thus define our problems and furnish a basis for therapeutic action. They do nothing, however, to explain the processes of aging. If we wish to understand these there is at present only one method available viz., homotransplantation, although future conditions can be envisaged in which other methods will become practicable.

SUMMARY

Albino rats were adrenalectomized at the age of 40 days. Their growth, reproduction, water diuresis, uropepsin excretion, and potassium tolerance were studied during the ensuing 143 days. No difference was discovered in these respects between animals bearing adrenocortical transplants from littermates and those bearing transplants from animals 280 days older. These findings are discussed and the impossibility of gathering exact information on aging processes by investigation on intact animals is analyzed.

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AN AGE DIFFERENCE IN PROPORTIONS OF CELL TYPES IN THE EPIDERMIS OF ABDOMINAL SKIN OF THE RAT*

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IN SEVERAL previous papers (2,3,5, and 6) we have reported on the occurrence of lymphocytes in the normal epidermis of the rat. Such cells have been found by us also in the epidermis of skin removed by biopsy from human subjects (5).

Our quantitative studies on lymphocytes and on clear cells in rats of middle age (300 days) had included epidermis both from the interscapular region of the back and from the abdomen (5) but our statistical study on such cells in young (21 day) and senile (900 day) rats concerned only the epidermis of the back (6). In this latter study no significant difference in the numbers of these cells at different ages was seen, although the variation in numbers is greater in the senile rats than in young or middle-aged ones.

An inspection of our figures for the lymphocytes, intermediate cells, and clear cells in the epidermis of skin from the abdominal region in the 300-day rats showed an apparently smaller number of "non-epidermal" cells, particularly of the lymphocytes, in this region than on the back. Since specimens of abdominal skin from all of the 21-day and all of the senile (900-day) rats were available for sectioning and staining, a study of this material was decided upon in order to ascertain 1) whether the difference in number of lymphocytes in epidermis of the back and of the abdomen is a consistent, statistically significant finding, and 2) whether the numbers of lymphocytes, intermediate cells, and clear cells in the abdominal region show any differences correlated with the age of the rats.

MATERIALS AND METHODS

The animals used in this study were 20 in number, 9 Wistar Institute Albino rats 21 days of age and 11 senile rats of the same strain, each 900 days of age. The skin specimens were taken from the abdomen near the midline, fixed in Bouin's or in 10 per cent formalin, dehydrated, cleared, and embedded in paraffin. Sections were cut at 5 μ. Preparations by several staining methods were made for each specimen. Four slides, each having several sections, were stained with hematoxylin and eosin, 2 with Mallory's triple stain, and 2 with Heidenhain's iron hematoxylin.

The method of classifying and counting of cells has been essentially similar to that used in two earlier studies (5,6). All observations and counts were made with the 97X oil immersion lens and 10X ocular. These counts necessarily contain a subjective and qualitative element, since the cells other than ordinary epidermal cells are placed in different categories depending on sometimes rather slight differences. Lymphocytes in the underlying dermis offer good objects for comparison with those in the epidermis, the only difference lying in the clear "halo" which generally surrounds the nucleus of the lymphocyte in the latter position (fig. 5). Clear cells usually are much larger than lymphocytes, almost equal in size to the adjoining "ordinary" epidermal cells. The cytoplasm is almost or entirely clear, sometimes of an opalescent appearance. The nucleus is vesicular. Nucleoli may or may not be present. The nuclear sap usually is darker than in ordinary epidermal cells (fig. 10). "Intermediate cell" is the term which we have used to apply to cells which seem to lie between the lymphocyte and the clear cell in their morphologic features such as size and staining characteristics, particularly of the nucleus (fig. 9).

A count was made of 1000 nuclei (cells) in the stratum germinativum of each animal. The results were tabulated and statistically analyzed to obtain the probable error of the mean for each of the two age groups studied (21 days and 900 days). It was considered worth while also to retabulate here and to analyze statistically for the first time the data from the study of abdominal skin of Wistar Institute rats 300 days old (5).

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OBSERVATIONS

The skin of the abdomen of the rat has been found to have a configuration considerably different from that of the back. There the surface is smooth, while on the abdomen a series of overlapping units are seen in the sections. These structures consist of a central core of dermis, covered above and below by epidermis (fig. 1 and 2). The dermal component hardly can be thought of as a papilla as it does not protrude into the epidermis in such a way as to create an unevenness in thickness of the latter layer. The arrangement as seen in our sections, where the skin is cut longitudinally, is very similar to that shown in sections of reptilian or avian scales.

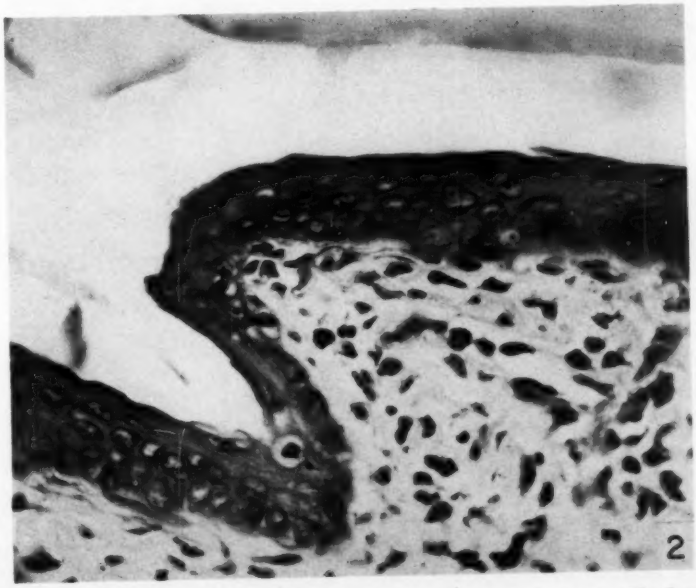
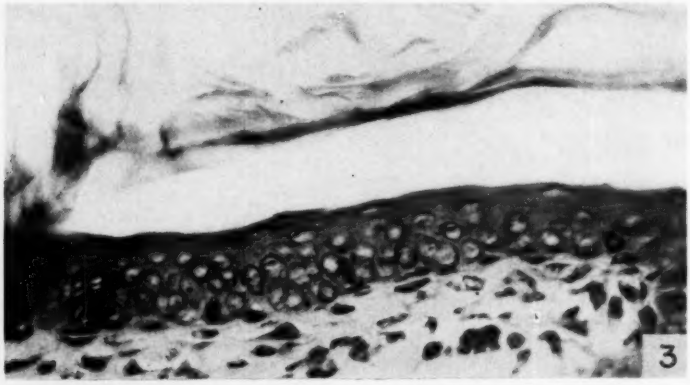


FIG. 1. Abdominal skin of a 21 day old male rat. The transverse ridges are seen. The hairs arise beneath these ridges. X110.

FIG. 2. A single ridge of the same specimen. Note the richly cellular dermis of the young animal. A clear cell is seen in a superficial position in the epidermis in the niche beneath the ridges. X450.

In order to obtain a clearer concept of this structure, we have studied the surface of the abdominal skin with the dissecting binocular microscope. Such study shows that there actually is a series of overlapping ridges which run transversely across the abdomen. The distance from the crest of one ridge to the next is about 0.5 mm. The transverse ridges are not, however, smooth, but show numerous secondary, rounded protrusions, reminding one again of individual scales in a row, although there is little regularity to the way in which these secondary protrusions occur. The hairs seem to arise invariably from the niches formed by these ridges and here the mouths of the sebaceous glands are seen (fig. 1). Whereas on the back the avoidance of hair follicles was somewhat of a problem in the study of the epidermis with the oil immersion lens, this arrangement on the abdomen, with a very clear-cut repetition of structures, aids one to avoid these follicles and to continue with the "uncomplicated" epidermis. For consistency, we began the counts in the niche and proceeded from there in each case.



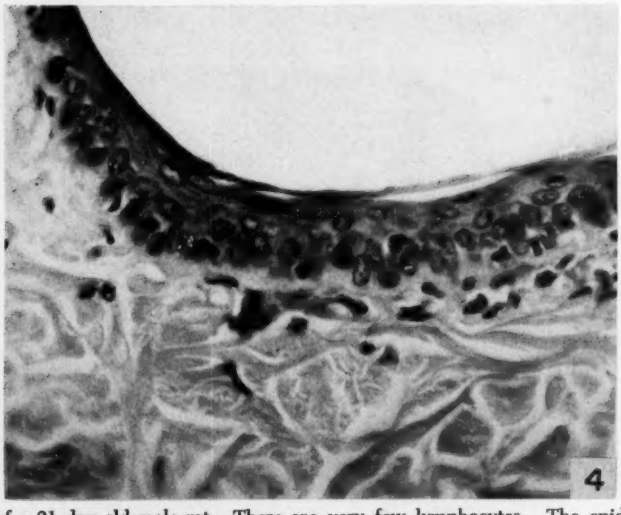
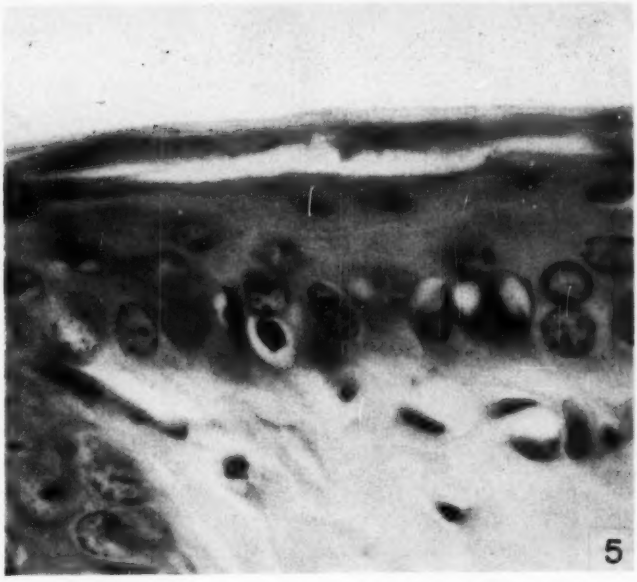


FIG. 3. Epidermis of a 21 day old male rat. There are very few lymphocytes. The epidermal nuclei show very little granular material and appear "crowded." X450.

FIG. 4. Epidermis of a 900 day female rat. A number of lymphocytes are seen in the basal layer. The epidermal nuclei contain many granules and are not "crowded." X450.



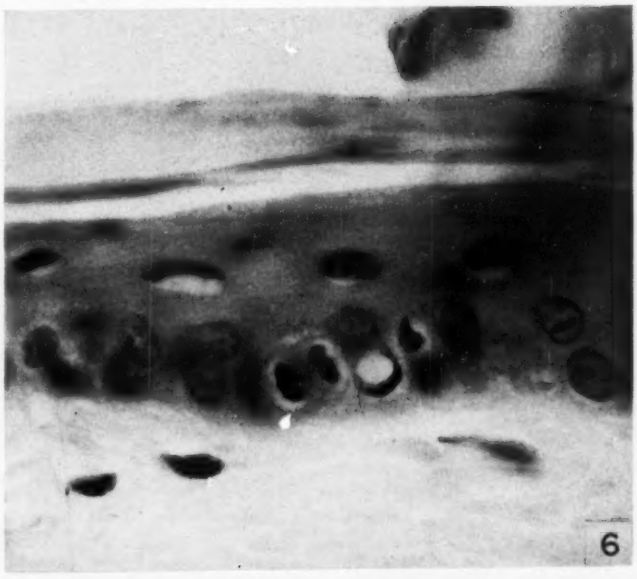
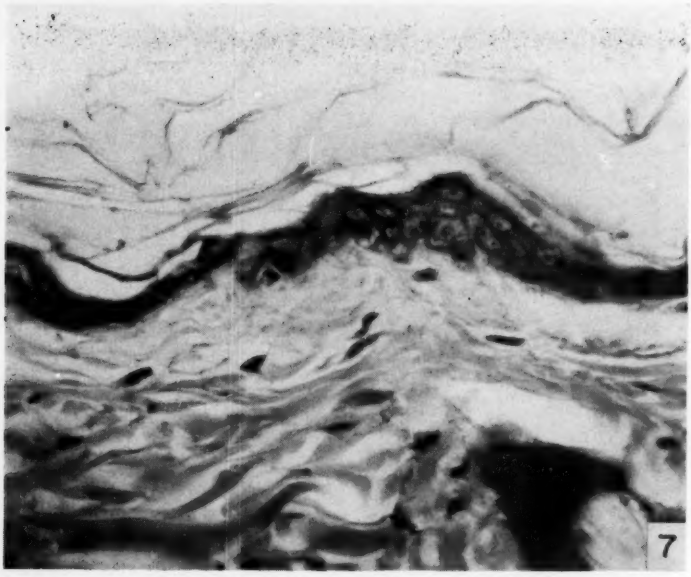


FIG. 5. Epidermis of a 900 day female rat. A lymphocyte is seen in the basal layer just to left of center. In senile animals the intraepidermal lymphocytes usually show very dense nuclei. Note the large vacuole-like space about the lymphocyte nucleus. Several of the epidermal cells show features seen usually only in the old rats, namely, vacuoles deforming their nuclei. X1050.

FIG. 6. Epidermis of the same specimen. A telophase in mitosis of an epidermal cell is shown. Mitosis, pecularily enough, seem to be more abundant in the epidermis of senile rats than in middle-aged and young animals. X1050.



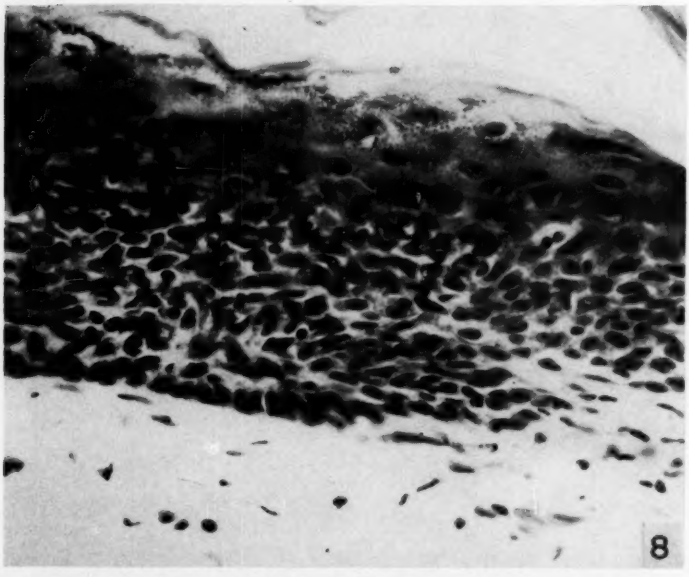
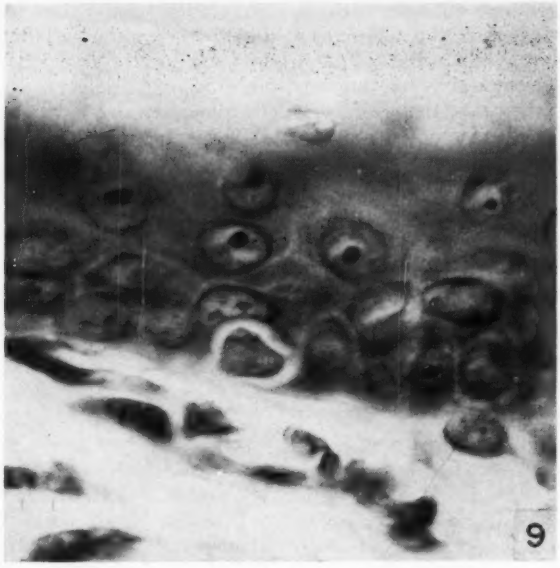


FIG. 7. Epidermis of a 300 day female rat. The clear nuclei and lack of a stratum granulosum distinguish it from the epidermis of senile animals. The paucity of cells in the dermis distinguishes the skin of middle-aged animals from that of very young animals. X450.

FIG. 8. An area of abdominal skin of a senile rat, a 900 day female. In some small areas in old rats a marked infiltration of the epidermis occurs and makes it difficult to obtain counts on the cell types present. X450.



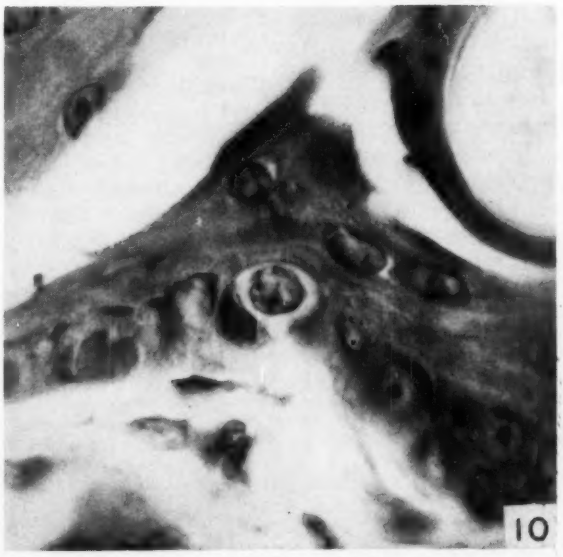


FIG. 9. Epidermis of a 21 day male rat. In the basal layer near the center of the field is seen an "intermediate" cell with clear cytoplasm and a nucleus which in morphologic characteristics lies between that of a lymphocyte and that of a clear cell. Note deformation of the epithelial nucleus above, apparently the effect of pressure by expansion of the intermediate cell. X1050.

FIG. 10. Epidermis of the same animal as in fig. 9. A clear cell is seen in the basal layer. The nucleus in this case resembles that of the epithelial cells, including a conspicuous nucleolus. Note the apparent pressure effects caused by this cell. X1050.

In spite of the architectural difference in the back and abdominal skin, the differences in both dermis and epidermis in the different age groups are very comparable for the two regions. In the 21 day rats the dermis is richly cellular and the fibers are delicate. In the middle-aged rats (300 days) this layer contains relatively few cells and the fibers are coarse. In the senile rats (900 days) the cell population of the dermis generally is scanty but there is more variation in this regard and in some localized regions there are considerable accumulations of wandering cells, both lymphocytes and polymorphonuclears.

The epidermis of the 21 day animal shows epithelial cells with large clear nuclei which appear to "crowd" the tissue (fig. 3). There is no stratum granulosum. The stratum cor-

TABLE 1. DATA OBTAINED BY COUNTS OF 1,000 CELLS PER ANIMAL FROM REGION OF ABDOMEN.

Identification	Age in Days	Sex	Lympho-cytes	Intermediate Cells	Clear Cells	Total Number of Mitotic Figures
			Young, Immature Rats			
671	21	M	1	6	129	0
672	21	F	3	9	93	0
690	21	M	5	8	98	0
692	21	M	2	9	274	1
693	21	F	2	3	152	0
695	21	M	12	23	95	1
696	21	F	4	3	76	0
699	21	M	5	4	152	0
700	21	F	5	11	145	2
			Middle-Aged Rats			
156	300	M	18	4	45	1
158	300	F	17	3	83	0
222	300	F	29	15	39	0
266	300	M	20	12	89	0
301	300	M	9	10	24	1
303	300	F	16	9	58	1
			Old Rats			
387	900	F	111	26	265	7
896	900	M	5	11	194	3
954	900	M	8	13	60	1
977	900	F	27	7	73	0
978	900	F	4	6	48	0
979	900	F	27	15	106	2
980	900	F	23	15	112	2
991	900	F	62	35	284	2
994	900	F	14	15	217	16
995	900	F	32	33	410	3
996	900	F	20	15	337	6

neum is composed of loosely adherent lamellae.

The epidermis of the 300 day rats is fairly similar to that of the very young animals (see fig. 7). Here the lymphocytes are more numerous, however. In both of these age-groups the invading lymphocytes have nuclei which seldom are densely compact.

In the senile rats the cytoplasm of the epithelial cells seems more abundant and conspicuous in relation to the nuclei (fig. 4, 5, and 6). There is a stratum granulosum, although the extent of this is variable. It is generally more prominent near to the crests of the ridges but appears also in other locations. The stratum corneum consists of closely adherent lamellae which are more eosinophilic than in the young and middle-aged animals. At the crests and on the descending slopes of the ridges, however, an interesting difference is seen. Here the lamellae are lightly basophilic and seem to be less closely adherent to each other. Whether this fact is dependent on the emergence of the hairs from beneath the ridges or whether it is simply an intrinsic part of the ridge pattern it is not possible for us to say.

The cell types in the epidermis of senile rats, other than the ordinary epidermal type, consist again of lymphocytes, intermediate cells, and clear cells. The nuclei of the intraepidermal lymphocytes are denser in appearance here than in younger animals but resemble them in other respects. The variation in the numbers of lymphocytes and of clear cells in individual animals and in different areas of the abdominal skin in the senile animals is striking. In a few places there seems to be a really massive infiltration and the distinction between the nuclei of different cell types becomes difficult (fig. 8).

The observations on the lymphocytes, intermediate cells, and clear cells in the abdominal region in all three age groups show certain definite similarities between these cells here and in the interscapular region. Here too the cells tend to deform the adjoining epithelial cells, apparently by a pressure effect (figs. 9 and 10). In this region also the cells show the same gradation in morphologic features from lymphocytes to clear cell in all age groups.

The differences between the abdomen and the back concern 1) the position of the cells, particularly of the clear cells, in the epidermis and 2) the numbers of the three cell types at different ages. In relation to the position, we have found larger numbers of clear cells at the angles of the cutaneous ridges. In this region too we frequently see such cells even in the superficial layers of the epidermis (fig. 2) an uncommon finding elsewhere in the abdominal epidermis and infrequently seen in the skin of the back.

In relation to the numbers of the cells of these three types in the different age groups, a survey of the figures in table 1 will show the small numbers of lymphocytes in the 21 day rats, the larger number in the 300 day rats, and in general fairly large, but greatly varying, numbers in the 900 day rats.

TABLE 2. DATA ON LYMPHOCYTES, INTERMEDIATE CELLS, CLEAR CELLS, AND MITOTIC FIGURES OF 3 AGE GROUPS IN REGION OF ABDOMEN OF WISTAR RATS.

The mean, with its probable error, and the range are given for each age group.

Age Groups	Lymphocytes	Intermediate Cells	Clear Cells	Mitotic Figures
21 Day (9 animals)	4.33 ± 0.73	8.44 ± 1.40	134.88 ± 11.24	0.33 ± .18
	1 – 12	3 – 23	76 – 274	0 – 2
300 Day (6 animals)	18.16 ± 1.94	8.83 ± 1.31	56.33 ± 7.50	.05 ± .15
	9 – 29	3 – 15	24 – 89	0 – 1
900 Day (11 animals)	30.27 ± 6.45	17.18 ± 2.12	191.45 ± 26.93	3.80 ± .84
	4 – 111	6 – 35	48 – 410	0 – 16

Table 2 presents the mean with its probable error for each age group. In spite of the considerable variations from animal to animal, it seems clearly established that the number of lymphocytes in the epidermis of abdominal skin of very young rats is significantly lower than in middle-aged or senile rats. Also, it is far lower than on the back of these same rats (6) (abdomen, 4.33 ± 0.73; back, 23.7 ± 1.43). It is also significantly lower for the abdomen in middle-aged rats than for the back (abdomen, 18.16 ± 1.94; back, 33.67 ± 2.55).

There may be a question about the significance of the difference in number of lymphocytes in the abdominal epidermis of middle-aged and senile rats, but the range and variation are definitely greater in the senile rats.

For the intermediate cells, the number given for the 900 day rats is significantly larger than for the 21 day and 300 day rats. A possible additional source of error must be admitted here, however, in that the assignment of these cells to a particular category involves more of a subjective element than for the other two types.

For the clear cells, it seems doubtful whether the differences, except between the middle-aged and the other two groups, are of significance. On the abdomen, however, as on the back, these constitute by far the most numerous cell type except for the ordinary epidermal cells. Here also, as on the back, the range in numbers of these cells among individuals is greatest in the senile rats.

The *higher* percentage of mitotic figures in senile animals is of interest, particularly as rats of 21 days are, of course, actively growing animals.

DISCUSSION

The chief result of this study on cell types in the epidermis of the abdominal skin of the rat has been to establish evidence of age difference in mean numbers for the lymphocytes, in particular the occurrence of much smaller numbers of these cells in young rats. This "age" difference is apparently a regional one for no such difference was found in a study of the skin of the back (6).

In addition to this finding, the present study has shown the appearance of the various cell types in the epidermis of the abdomen to be similar to that on the back. Observations here have shown no more evidence of any degeneration of the lymphocytes within the epidermis than in the interscapular region. The question again is raised as to the ultimate fate of these motile cells after they have wandered into a layer of non-motile elements such as the ordinary epidermal cells.

The problem of the migration of motile cells into epithelia has been of much interest to us. In earlier studies (4, 7, and 8) we have described the lymphocytes in the intestinal epithelium in the mouse. The general phenomenon of migration of lymphocytes into the epithelial lining of various organs has been recognized previously (10) and we have cited the literature and the interpretations by various workers in our own previous papers.

Careful consideration of the phenomena observed in the intestine led us eventually to the conclusion that these motile cells in some way probably furnish new cells of the epithelial layer (1), as difficult as the theoretic implications of this conclusion seemed. Since that time we have studied the method of replacement and differentiation of the intestinal epithelium in the tailed amphibians or Urodeles (9). Here there is a clear-cut process of *migration* of relatively undifferentiated cells from cell nests lying at varying levels beneath the surface and a differentiation of these cells into ordinary epithelial cells and goblet cells as they arrive at the surface. The cell nests show a considerable variety in structure of the constituent nuclei and include a number of a compact type which may well be of mesodermal origin.

While admittedly there is a great dissimilarity between the intestine of the salamander and the skin of the rat, this recent study has presented us with the occurrence of a phenomenon which in its basic principle seems to follow very well the hypothesis which we have advanced for the role of the lymphocytes in the epidermis, namely, a migration of cells into an epithelial layer, followed by a "settling down" and differentiation there to become an integral part of that layer.

SUMMARY

1. A quantitative study has been made of the lymphocytes, clear cells and "intermediate" cells in the epidermis of the abdomen of 20 Wistar Institute rats at ages ranging from 21 days to 900 days.

2. There is a significantly smaller number of lymphocytes, relative to number of epidermal cells, on the abdomen than on the back in the young and middle-aged rats.

3. There is a significantly smaller number of lymphocytes in the abdominal epidermis of 21 day rats than in that of 300 or 900 day rats.

4. Comments on the appearance and numbers of the other cell types, for which the quantitative data are not as clear-cut, are given.

5. No evidence is seen of degeneration of lymphocytes in the epidermis of the abdominal skin and the question of their fate here again is posed.

6. In light of recent studies on the replacement of epithelium in the intestine of the Urodeles, the feasibility of the concept of a migration into epithelial layers, followed by a differentiation, of motile elements to become integral parts of these layers, is reasserted.

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VARIATION WITH AGE IN THE FUMARASE ACTIVITY OF HUMAN AORTIC AND PULMONARY ARTERY TISSUE*

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IN A RECENT publication from this laboratory (2) the presence of fumarase in the human aorta was demonstrated. Since a tendency was noted for the fumarase activity of the arterial tissue to decrease with advancing age of the individuals it was decided to subject the relationship between age and the fumarase activity of the tissue to a more detailed study and to extend the investigation to include, besides samples of the human aorta, preparations of the pulmonary artery from the same persons.

METHODS

One hundred and seven samples of the human thoracic aorta and 95 samples of the pulmonary artery were obtained fresh at autopsy at the St. Louis City Morgue.† The age of the individuals from whom the samples were derived ranged between 3 weeks and 92 years. Immediately after removal the samples were placed in sterile beakers immersed in crushed ice. After separation of the adventitia the intima-media segments were rinsed with water to remove adherent blood. The samples were subsequently homogenized in a pyrex grinder with 9 volumes of distilled water, making a 10 per cent homogenate.

The determination of the fumarase activity of the homogenates was carried out by a modification of the previously described fluorometric method (2). The main improvement in the technique consisted in the employment of a stable, aqueous beta-naphthol reagent, instead of the alkaline beta-napthol reagent used in the original method of Lowry and associates (3). For preparation of the standard 1-malic acid recrystallized twice from hot ethyl acetate was employed. A detailed description of the modified technique for 1-malic acid determination will be given elsewhere. The enzyme measurements, including the blank determinations, were performed in duplicate, using 1.0 and 2.0 ml. homogenate samples. The average difference between duplicate measurements was 7.2 per cent. A 30-minute incubation period was used in all the experiments.

In the case of both the aortic and pulmonary artery samples determinations of the dry weight, total nitrogen and cholesterol content of the tissue were made on portions of the arterial wall adjacent to those employed for the enzyme studies. The nitrogen analyses were carried out by conventional Kjeldahl technique. For the cholesterol determinations the procedure of Knobil and associates (1) was used.

RESULTS

Aortic Samples.—The results of the individual fumarase determinations on the 107 aortic samples are presented in table 1. The table further contains the observed dry weight, total nitrogen, and cholesterol values for the samples. In addition, the grading of the samples on the basis of their macroscopic appearance has been included.

The average 1-malic acid formation for the 107 aortic samples was 8.95 mg./Gm. wet tissue/30 min. The fumarase activity of the samples derived from the women was 97 per cent of the values observed for the men in the corresponding age groups.

The mean fumarase values found for the various decades have been listed in table 2. It will be seen from the data presented in the table that the 1-malic acid formation by the aortic samples was found to decrease from a value of 14.6 mg./Gm. wet tissue/30 min. for the 0-9 year old group to about half that value for the subjects aged 60 years and over. A calculation of the coefficient of correlation between the age of the individuals and the 1-malic acid formation by the tissue shows the following values:

Age/1-malic acid formation/Gm.wet tissue

$$r = -0.63,\ t = 8.26,\ N = 107$$

Age /1-malic acid formation/Gm. tissue nitrogen

$$r = -0.39,\ t = 4.27,\ N = 105$$

Since comparatively little change in the tissue fumarase activity was found for the age range 55 to 79 years it was decided to subject the data for this group of samples to a more detailed analysis. The results of an evaluation of the correlation between the degree of arteriosclerotic changes in the tissue as judged by macroscopic inspection and the

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†The authors are indebted to Dr. J. J. Connor for assistance in obtaining specimens.

TABLE 1. FUMARASE ACTIVITY OF 107 HUMAN AORTIC SAMPLES.

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	1-Malic Acid Formation		Macroscopic Arteriosclerosis
							Mg./Gm. Wet Tissue/ 30 Min.	Mg./ Gm.N/ 30 Min.	
1	0.08	M	C	26.0	4.51	0.58	26.0	577	none
2	0.25	M	W	29.0	5.27	0.26	15.8	300	none
3	0.42	F	W	27.2	4.48		13.9	311	none
4	0.50	F	C	28.9	4.73	0.34	8.8	186	none
5	0.50	M	W	27.9	4.60	0.27	16.5	359	none
6	0.75	F	C	27.1	4.57	0.24	11.0	242	none
7	1.50	F	W	29.3	5.21	0.44	9.4	181	none
8	1.50	F	W				13.3		none
9	3	M	W				13.1		none
10	3	M	W	33.5	5.52	0.70	18.6	347	none
	Mean.....			36.1	4.86	0.40	14.6	308	
11	14	M	W	28.4	4.50	0.63	9.0	200	slight
12	14	M	W	28.5	4.48	0.66	10.7	239	slight
13	16	M	W	28.7	4.13	0.68	16.6	402	slight
	Mean.....			28.5	4.37	0.66	12.1	280	
14	21	M	W	27.4	4.32	1.17	11.2	259	slight
15	22	F	C	27.0	4.07	0.36	7.4	182	slight
16	24	M	W	29.4	4.38	1.11	13.5	308	moderate
17	27	M	C	27.4	4.09	0.98	16.2	396	none
	Mean.....			27.9	4.21	0.91	12.1	286	
18	33	M	W	28.3	4.06	1.00	14.0	345	slight
19	33	M	C	28.0	4.83	1.07	11.4	236	slight
20	34	M	W	23.4	3.51	1.35	6.5	185	
21	35	F	C	24.7	4.02	1.26	15.9	396	none
22	36	M	W	25.4	3.66	0.80	8.9	243	none
23	37	M	C	25.8	3.90	0.48	7.1	182	none
24	37	F	W	28.7	3.10	0.76	10.7	345	none
25	37	M	C	24.2	3.45	0.53	5.9	171	slight
26	38	M	W	22.6	3.61	1.02	13.0	360	none
27	39	M	W	25.3	3.61	1.12	11.8	327	none
28	39	M	W	25.2	3.55	1.60	15.5	437	moderate
	Mean.....			25.6	3.75	1.00	11.0	293	
29	43	M	W	25.2	3.74	0.84	8.5	227	
30	44	M	W	23.9	3.73	0.76	8.2	219	slight
31	44	M	W	24.8	3.44	2.00	10.4	302	moderate
32	45	F	C	27.4	3.89	0.96	5.3	136	none
33	45	F	W	24.1	3.51	1.10	8.2	234	none
34	47	M	W	28.6	3.44	1.44	9.2	268	
35	47	M	W	23.9	3.35	0.74	9.0	269	
36	47	M	W	24.9	3.47	4.28	10.6	306	severe
37	48	M	C	24.3	3.59	0.63	7.8	216	none
38	48	M	W	23.6	3.28	1.46	7.9	241	moderate
39	48	M	W	22.7	3.07	2.50	9.1	296	moderate
40	49	M	W	25.3	3.13	1.02	10.6	339	slight
41	49	F	W	23.5	2.88	0.87	11.0	382	slight
	Mean.....			24.8	3.43	1.43	8.9	264	
42	50	M	C	25.0	3.17	1.33	5.9	186	moderate
43	50	M	W	24.8	3.76	0.82	9.3	247	
44	50	M	W	26.9	3.75	0.86	6.9	184	none
45	51	F	W	25.7	3.73	0.90	7.2	192	slight

TABLE 1—Continued

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	1-Malic Acid Formation		Macroscopic Arteriosclerosis
							Mg./Gm. Wet Tissue/ 30 Min.	Mg./ Gm.N/ 30 Min.	
46	51	M	W	26.4	3.43	1.48	5.9	172	moderate
47	52	M	W	24.6	3.47	1.19	8.1	234	moderate
48	52	M	W	24.0	3.39	2.18	15.0	442	moderate
49	53	M	W	23.5	3.23	0.83	10.1	312	moderate
50	53	M	W	25.1	2.70	2.76	10.7	396	
51	54	M	W	25.6	3.81	0.60	8.5	223	slight
52	54	M	W	26.0	3.37	1.68	10.0	297	moderate
53	54	M	C	30.0	3.42	1.28	5.2	152	
54	54	M	W	24.0	3.48	1.50	11.4	330	
55	55	M	W	24.8	3.07	0.70	7.2	235	
56	55	M	C	21.3	3.29	1.10	5.9	179	moderate
57	55	M	W	28.0	3.66	3.25	1.7	47	severe
58	56	M	W	23.8	3.20	5.60	3.5	109	severe
59	57	M	W	24.2	3.21	2.54	9.1	284	moderate
60	57	F	W	26.4	3.37	1.14	7.5	223	slight
61	57	M	W	26.7	3.30	3.50	6.8	206	severe
62	58	F	W	25.1	3.42	2.12	9.6	281	severe
63	58	M	W	23.8	3.20	1.76	6.7	209	moderate
64	58	M	W	26.3	3.19	4.96	4.7	147	
65	58	F	W	23.9	3.35	0.55	6.0	179	
66	59	M	W	25.5	3.48	0.87	13.3	384	none
67	59	M	W	32.2	3.32	2.70	6.5	196	severe
	Mean.....			25.5	3.38	1.85	7.8	232	
68	60	M	W	23.5	3.21	3.53	7.4	231	severe
69	60	M	W	26.2	3.57	1.12	10.7	300	severe
70	60	M	W	23.4	3.32	1.28	7.3	220	moderate
71	61	M	W	28.3	2.72	4.19	7.7	284	severe
72	62	M	W	24.1	3.32	1.48	7.9	238	
73	63	M	W	27.2	3.45	2.40	5.0	145	moderate
74	64	M	C	24.8	3.26	2.38	9.6	294	slight
75	64	M	W	26.1	3.33	3.57	6.6	198	moderate
76	64	M	W	21.9	3.08	0.94	7.4	240	moderate
77	65	M	W	25.4	3.02	4.46	11.8	391	severe
78	65	M	W	31.3	3.59	3.50	4.7	131	severe
79	65	M	C	28.7	3.65	2.02	6.7	184	
80	65	M	C	25.4	3.42	3.44	6.7	196	
81	65	M	W	24.4	3.26	2.24	10.9	334	moderate
82	65	M	C	25.7	3.47	1.44	4.9	141	moderate
83	65	M	W	23.2	3.16	0.99	8.0	253	slight
84	67	F	C	26.5	2.83	2.53	4.4	155	severe
85	67	M	W	21.0	3.08	1.80	8.6	279	severe
86	69	M	C	25.3	3.13	2.74	5.4	173	severe
87	69	M	W	27.2	2.96	3.60	6.0	203	
	Mean.....			25.5	3.24	2.37	7.4	230	
88	70	M	C	25.9	3.51	1.62	11.2	310	slight
89	72	M	W	26.4	3.27	3.45	8.6	263	severe
90	72	F	W	23.3	2.93	2.40	10.3	352	moderate
91	72	M	W	27.7	3.28	2.50	5.8	177	severe
92	72	M	W	24.8	3.45	1.30	5.3	153	
93	72	F	W	26.6	3.46	3.60	5.4	156	
94	73	F	W	24.1	3.30	2.30	1.4	43	severe
95	73	M	W	27.4	3.28	1.80	10.9	332	moderate
96	74	F	C	26.6	3.39	2.30	5.2	153	severe
97	74	M	C	27.2	3.56	1.51	3.2	90	moderate
98	75	M	C	24.1	3.33	0.72	9.8	294	slight
99	75	F	W	25.7	3.38	4.10	6.3	186	

TABLE 1—Continued.

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	1-Malic Acid Formation		Macroscopic Arteriosclerosis
							Mg./Gm. Wet Tissue/30 Min.	Mg./Gm.N/30 Min.	
100	75	M	W	29.8	2.98	4.38	7.4	248	severe
101	79	M	W	28.0	2.73	2.44	7.4	271	
	Mean			26.3	3.27	2.46	7.0	217	
102	80	M	W	25.0	3.23	1.10	5.7	176	slight
103	80	M	C	23.0	3.29	0.62	8.7	264	
104	81	M	W	26.3	3.25	0.76	7.5	231	slight
105	87	M	W	28.3	3.31	2.46	4.4	133	severe
106	88	F	W	28.2	3.29	4.60	9.1	277	severe
	Mean			26.2	3.27	1.91	7.1	216	
107	92	M	C	25.4	3.18	1.16	5.7	179	slight
	Grand Mean			26.5	3.55	1.72	8.95	248	

TABLE 2. 1-MALIC ACID FORMATION BY HUMAN AORTIC TISSUE IN VARIOUS DECADES.

Age Group (Years)	Number of Samples	Mean 1-Malic Acid Formation	
		Mg./Gm. Wet Tissue/30 min.	Mg./Gm. Tissue N/30 min.
0–9	10	14.6	308
10–19	3	12.1	280
20–29	4	12.1	286
30–39	11	11.0	293
40–49	13	8.9	264
50–59	26	7.8	232
60–69	20	7.4	230
70–79	14	7.0	217
80–92	6	6.9	196
	107	Mean 8.95	248

fumarase activity are presented in table 3. It will be seen from the table that a tendency was observed for the fumarase activity to decrease with the degree of arteriosclerosis present. It will further be noted that a good agreement was found between the macroscopic evaluation of the samples and the cholesterol tissue values found. A calculation of the coefficient of correlation between the tissue cholesterol content and the 1-malic acid formation by the samples for this age range showed an r value of -0.24 ($t = 1.66$, $N = 47$).

TABLE 3. CORRELATION BETWEEN DEGREE OF ARTERIOSCLEROSIS OF HUMAN AORTIC SAMPLES FOR INDIVIDUALS AGED 55-79 YEARS AND FUMARASE ACTIVITY OF TISSUE.

Degree of Macroscopic Arteriosclerosis	Number of Samples	Average Cholesterol Content of Tissue % of Wet Weight	Average 1-Malic Acid Formation Mg./Gm. Wet Tissue/30 min.
None	1	0.87	13.3
Slight	5	1.37	9.3
Moderate	12	1.92	7.4
Severe	18	2.94	6.5

TABLE 4. FUMARASE ACTIVITY OF 95 SAMPLES OF HUMAN PULMONARY ARTERY.

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	1-Malic Acid Formation		Macroscopic Arteriosclerosis
							Mg./Gm. Wet Tissue/30 Min.	Mg./Gm.N/30 Min.	
3	0.42	F	W	26.0	4.01		24.6	611	None
5	0.50	M	W	32.4			14.5		None
9	3	M	W				16.8		None
	Mean			29.2	4.01		18.6	611	
13	16	M	W	27.8	4.32	0.58	17.1	396	None
16	24	M	W	26.3	4.10	0.22	18.4	448	None
17	27	M	C	27.7	4.11	0.62	34.5	838	None
	Mean			27.0	4.11	0.42	26.5	643	
18	33	M	W	24.1	3.74	0.74	16.5	441	None
19	33	M	C	30.4	4.66	0.44	20.2	434	None
20	34	M	W	24.3	4.10	0.60	10.7	261	
21	35	F	C	24.6	4.12		24.8	602	None
22	36	M	W	22.1	3.26	0.92	14.1	432	None
23	37	M	C	25.0	4.14	0.40	10.3	249	None
25	37	M	C	25.4	3.92	0.46	36.9	940	None
26	38	M	W	23.8	3.82	0.38	11.8	419	None
27	39	M	W	25.3	3.47	0.80	16.5	476	None
28	39	M	W	25.4	3.83	0.86	20.2	527	None
	Mean			25.7	3.91	0.62	18.2	471	
29	43	M	W	24.7	3.73	0.76	13.3	356	
30	44	M	W	28.3	4.49	0.50	12.5	278	None
31	44	M	W	22.8	3.50	1.14	13.9	397	None
32	45	F	C	21.8	3.30	1.00	8.7	264	None
33	45	F	W	27.0	4.30	0.71	11.9	277	None
34	47	M	W	24.4	3.73	0.74	11.1	297	
35	47	M	W	27.5	4.14	0.36	16.6	401	
36	47	M	W	23.2	2.89	2.05	15.5	536	Moderate
37	48	M	C	26.9	4.24	0.51	15.1	356	None
38	48	M	W	19.3	2.82	0.50	12.3	435	None
39	48	M	W	27.6	4.24	0.78	17.3	408	None
40	49	M	W	28.0	.419	0.69	18.5	442	None
41	49	F	W	23.2	3.32	0.37	25.3	764	None
	Mean			24.9	3.76	0.78	14.8	401	

TABLE 4—Continued.

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	1-Malic Acid Formation		Macroscopic Arteriosclerosis
							Mg./Gm. Wet Tissue/30 Min.	Mg./Gm.N/30 Min.	
42	50	M	C	21.9	3.32	0.49	10.6	320	None
43	50	M	W	23.6	4.29	0.56	15.8	369	
44	50	M	W	23.3	3.23	0.66	6.9	214	None
45	51	F	W	26.3	4.07	0.89	11.7	288	None
46	51	M	W	29.2	4.60	0.69	9.5	207	None
47	52	M	W	23.8	3.58	0.95	10.3	288	None
48	52	M	W	23.7	3.43	0.92	16.4	476	Slight
49	53	M	W	25.4	3.80	0.87	13.4	353	None
50	53	M	W	25.5	3.85	0.88	14.0	363	
51	54	M	W	22.9	3.53	0.60	9.9	281	None
52	54	M	W	26.9	4.09	0.32	15.2	372	None
53	54	M	C	22.5	3.42	0.40	11.5	336	
54	54	M	W	24.7	3.82	0.90	14.4	376	
55	55	M	W	19.6	3.03	0.64	7.5	248	
56	55	M	C	23.8	3.92	0.79	10.6	271	None
57	55	M	W	22.4	3.38	0.80	10.9	322	None
58	56	M	W	23.6	3.23	0.46	14.3	443	None
59	57	M	W	23.7	3.45	1.62	24.8	720	Slight
60	57	F	W	25.3	3.92	0.60	9.2	234	None
61	57	M	W	23.4	3.43	0.55	11.8	343	None
62	58	F	W	21.5	3.02	0.94	13.7	454	None
63	58	M	W	23.6	3.28	1.16	11.5	350	Slight
64	58	M	W	19.8	2.94	0.46	12.1	412	
65	58	F	W	21.2	3.26	0.55	11.5	352	
66	59	M	W	25.1	2.43	1.12	14.6	601	Slight
67	59	M	W	24.4	3.59	1.16	8.8	244	None
	Mean.....			23.8	3.53	0.77	12.3	355	
68	60	M	W	22.9	3.41	1.60	13.1	384	Slight
69	60	M	W	23.5	3.47	0.61	16.3	470	None
70	60	M	W	21.3	3.15	0.54	15.1	477	None
71	61	M	W	27.4	3.68	0.44	11.7	318	None
72	62	M	W	24.0	3.17	0.76	14.2	446	
73	63	M	W	24.3	3.15	1.15	5.0	158	None
74	64	M	C	20.9	3.08	1.34	10.4	337	None
75	64	M	W	24.8	3.62	1.08	13.1	361	None
76	64	M	W	24.1	3.84	0.66	12.8	334	None
77	65	M	W	30.8	4.38	1.20	13.8	315	None
78	65	M	W	23.7	3.22	1.10	11.7	362	Slight
79	65	M	C	26.9	3.88	0.76	11.5	296	
80	65	M	C	21.9	3.56	0.76	11.3	317	
81	65	M	W	19.9	2.86	0.80	14.6	511	None
82	65	M	C	25.0	3.47	1.78	7.9	228	None
83	65	M	W	24.3	3.42	0.98	14.9	435	None
84	67	F	C	18.4	2.87	1.08	8.3	291	None
85	67	M	W	21.9	3.33	0.28	10.6	319	None
86	69	M	C	21.0	3.08	0.96	12.1	392	None
87	69	M	W	28.4	4.10	1.10	12.1	295	
	Mean.....			23.7	3.43	0.95	12.0	352	
88	70	M	C	24.3	3.30	0.98	14.6	442	None
89	72	M	W	25.4	3.50	1.31	12.0	334	None
90	72	F	W	22.0	3.19	0.61	16.7	524	None
91	72	M	W	21.1	4.53	1.18	10.7	237	None
93	72	M	W	22.8	3.42	0.44	9.1	266	
93	72	F	W	22.9	3.21	0.70	9.8	304	
94	73	F	W	23.0	3.29	0.60	15.2	461	Moderate
95	73	M	W	22.5	3.08	1.17	13.7	445	None
96	74	F	C	24.4	3.60	0.68	11.8	328	None
97	74	M	C	22.9	3.33	0.68	9.3	279	None
98	75	M	C	21.4	2.96	0.98	11.9	402	Slight

TABLE 4—Continued.

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	1-Malic Acid Formation		Macroscopic Arteriosclerosis
							Mg./Gm. Wet Tissue/30 Min.	Mg./Gm.N/30 Min.	
99	75	F	W	20.3	3.18	0.78	10.2	320	
100	75	M	W	24.0	3.39	2.24	12.9	380	Slight
101	79	M	W	23.3	3.01	0.78	13.9	461	
	Mean.....			22.9	3.37	0.94	12.3	369	
102	80	M	W	19.8	2.92	0.59	6.8	233	None
103	80	M	C	21.6	2.83	0.61	10.1	356	
104	81	M	W	22.4	3.33	0.52	10.8	323	None
105	87	M	W	21.2	3.17	0.75	7.3	230	None
106	88	F	W	23.3	3.31	1.56	7.3	220	None
	Mean.....			21.7	3.11	0.81	8.5	273	
107	92	M	C	21.4	2.91	1.36	8.2	282	Moderate
	Grand Mean....			24.1	3.56	0.81	13.5	380	

TABLE 5. 1-MALIC ACID FORMATION BY HUMAN PULMONARY ARTERY TISSUE IN VARIOUS DECADES.

Age Group (Years)	Number of Samples	Mean 1-Malic Acid Formation	
		Mg./Gm. Wet Tissue/30 min.	Mg./Gm. Tissue N/30 min.
0–29.....	6	21.0	575
30–39.....	10	18.2	471
40–49.....	13	14.8	401
50–59.....	26	12.3	355
60–69.....	20	12.0	352
70–79.....	14	12.3	369
80–92.....	6	8.4	274
	95	Mean 13.5	380

Pulmonary Artery Samples.—The results of the individual fumarase determinations on the 95 pulmonary artery samples are listed in table 4. The average 1-malic acid formation observed for the samples was 13.5 mg./Gm. wet tissue/30 min. The fumarase activity of the samples derived from the women was 111 per cent of the values observed for the men in the corresponding age groups.

A comparison of the individual data listed in tables 1 and 4 reveals that the fumarase activity of the pulmonary artery in all the cases was higher than that of the aorta from the same subject.

The mean fumarase values found for the various age groups have been listed in table

5 and show a similar decrease in enzyme activity with age as observed for the aortic samples. Thus the mean 1-malic acid formation by the pulmonary artery tissue was found to decrease from 21.0 mg./Gm. wet tissue/30 min. for children and young adults to about 12 mg. for the 50-79 year old subjects; for the oldest individuals (80-92 years) the average value found was only 8.4 mg. A calculation of the coefficient of correlation between the age of the subjects and the 1-malic acid formation by the tissue shows the following values:

Age/ 1-malic acid formation/Gm. wet tissue

$$r = -0.48, t = 5.26, N = 95$$

Age/ 1-malic acid formation/Gm. tissue nitrogen

$$r = -0.28, t = 2.80, N = 93$$

DISCUSSION

The stability of fumarase (2) and its independence of cofactors insure reliability of the tissue enzyme measurements. The data reported in the present study confirm the observations of the previous investigation (2) that the fumarase activity of human aortic tissue tends to decline with advancing age. The coefficients of correlation : Age/fumarase activity found in the two studies were −0.62 and −0.63, respectively. The absolute values observed for the 1-malic acid formation by the aortic tissue were in general somewhat higher in the present than in the previous investigation. This difference may to some extent be explained by the introduced improvements in the analytic technique.

The analysis of the relation between the degree of arteriosclerotic changes in the vessel and the enzyme activity, carried out for the aortic samples derived from individuals aged 55 to 79 years, revealed a negative correlation between the degree of arteriosclerosis present in the tissue and the fumarase activity. Since the amount of undamaged active tissue present in these samples is not known, it cannot be stated whether the fumarase activity of the unimpaired portions of the arteriosclerotic areas was lower than that of the apparently normal sections of the same vessel. It is possible that some information on this point may be obtained by comparison of the fumarase activity of small selected portions of the vessel wall with the histologic appearance of the same sections.

The fact that the fumarase activity of the aortic samples was found to decline from the 0-9 year age group to the 30-39 year group before the development of a notable degree of arteriosclerosis suggests that other factors besides arteriosclerosis are of significance in causing such decline. The finding in the case of the pulmonary artery samples of a similar decrease in fumarase activity with age supports the contention that the lower fumarase values are not merely the result of arteriosclerotic tissue changes, since the degree of arteriosclerosis observed in these samples on the whole was small. These considerations do not reflect on the possibility that a decrease in fumarase activity may be one of the factors contributing to the development of arteriosclerosis in the vessel wall.

SUMMARY

Determinations were made of the fumarase activity of 107 samples of the human thoracic aorta and 95 samples of the pulmonary artery. The age of the individuals from whom the samples were derived ranged between 3 weeks and 92 years. The analyses were performed by a modification of the procedure by Lowry and associates. The average 1-malic acid formation by the aortic samples was 8.95 mg./Gm. wet tissue/30 min., and by the pulmonary artery samples 13.5 mg./Gm. wet tissue/30 min. The fumarase activity of the pulmonary artery in all the samples studied was higher than that of the aorta from the same individual.

In agreement with the findings in a previous study the fumarase activity of the aortic samples was found to decrease with age, the coefficient of correlation : Age/1-malic acid formation being −0.63. For the pulmonary artery samples the corresponding r value was −0.48.

The significance of these findings is discussed.

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THE BETA-GLUCURONIDASE ACTIVITY OF AORTIC AND PULMONARY ARTERY TISSUE IN INDIVIDUALS OF VARIOUS AGES*

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The presence of beta-glucuronidase in the walls of arteries and veins of the rat was recently demonstrated by Seligman and associates (6) by histochemical procedures. In contrast to this, earlier studies by Friedenwald and Becker (3) had failed to reveal glucuronidase activity in the blood vessels of the rat liver. No reports are as yet available on quantitative measurements of the glucuronidase activity of vascular tissue.

The present study was undertaken with the purpose of determining the beta-glucuronidase activity of homogenates prepared from the human aorta and pulmonary artery from individuals of various ages. In addition, glucuronidase measurements on a limited number of coronary artery samples from young subjects were carried out.

METHODS

One hundred samples of the human thoracic aorta and 44 samples of the pulmonary artery were obtained fresh at autopsy at the St. Louis City Morgue.† The age of the individuals from whom the samples were derived ranged between 3 days and 88 years. Immediately after removal the samples were placed in sterile beakers immersed in crushed ice. After separation of the adventitia the intima-media segments were rinsed with water to remove adherent blood. The samples were subsequently homogenized in a Pyrex grinder with 9 volumes of distilled water, making a 10 per cent homogenate.

For study of the coronary artery system hearts were secured at autopsy from 16 subjects, ranging in age between 3 and 39 years. The coronary arteries were isolated by careful dissection, and homogenates of the tissue prepared as described above.

Determination of the beta-glucuronidase activity of the arterial homogenates was performed as described by Talalay, Fishman, and Huggins (7). The homogenate was centrifuged for 10 minutes at 3000 r.p.m., and 0.1 ml. aliquots of the supernatant employed for measurement of the enzyme activity. The aliquot was incubated for 16 to 18 hours at 38 C. with 0.8 ml. of acetate buffer, pH 4.5, and 0.1 ml. of a 0.01 M solution of phenolphthalein glucuronide (Sigma Chemical Co.). A small thymol crystal was placed in each tube during the incubation; it was ascertained that such addition did not measurably affect the enzyme activity.

At the end of the incubation period 1.0 ml. of a 5 per cent trichloroacetic acid solution was added, after which the sample was centrifuged for 10 minutes. The supernatant was then decanted into a test tube. The receiving tube, graduated at 6.0 ml. volume, contained 2.0 ml. of 0.2 M glycine buffer, pH 10.45, and 0.5 ml. of 0.5 N sodium hydroxide solution. The precipitate was rinsed with distilled water to remove any phenolphthalein adsorbed to the protein precipitate, and the wash water after centrifugation added to the supernatant in the receiving tube. The washing of the precipitate was carried out three times. The volume of the sample in the receiving tube was finally made up to 6.0 ml. with distilled water, and the quantity of phenolphthalein present determined spectrophotometrically at 550 $\mu\mu$. The glucuronidase activity of the tissue was expressed in the enzyme units employed by Fishman, Springer, and Brunetti (2), 1 glucuronidase unit corresponding to the liberation of 1 microgram of phenolphthalein in 1 hour at 38 C. from phenolphthalein glucuronide under the standard conditions used in the procedure.

All determinations were carried out in duplicate. The average difference between duplicate measurements was 5.8 per cent.

A blank analysis was run with each arterial sample. For the blank determinations the reagents were incubated at 38 C. for 16 to 18 hours, after which trichloroacetic acid was added, followed by the tissue homogenate. No measurable phenolphthalein liberation from the substrate was observed in the blank analyses.

In agreement with the observations by Talalay, Fishman, and Huggins (7) a good proportionality was found between the quantity of tissue present in the sample and the amount of phenolphthalein liberated by the enzyme activity. Linearity was also observed over a period of 20 hours between the time of incubation and the quantity of phenolphthalein glucuronide hydrolyzed.

In the case of both the aortic and pulmonary artery samples determinations of the dry weight, total nitrogen, and cholesterol content of the tissue were made on portions of the arterial wall adjacent to those employed for the enzyme studies. The nitrogen analyses were carried out by conventional Kjeldahl technique. For the cholesterol determinations the procedure of Knobil and associates (4) was used.

RESULTS

Aortic and Pulmonary Artery Samples.— The results of the individual glucuronidase

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determinations on the 100 aortic and 44 pulmonary artery samples are presented in tables 1 and 2, respectively. The tables further contain the observed dry weight, total nitrogen, and cholesterol values for the samples. In addition, the grading of the samples on the basis of their macroscopic appearance has been included.

TABLE 1. BETA GLUCURONIDASE ACTIVITY OF 100 HUMAN AORTIC SAMPLE

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	Glucuronidase Units/Gm. Wet Weight	Glucuronidase Units/Gm. Tissue N	Macroscopic-Arteriosclerosis
1	0.01	F	W				0	0	None
2	0.5	M	C	29.4	4.63	0.39	89	1920	None
3	1.5	F	W				27		None
4	3	M	W				2		None
5	3	M	W	33.5	5.52	0.70	42	750	None
6	5	F	C	24.7	3.95	0.33	16	405	None
	Mean.....			29.2	4.70	0.47	29	770	
7	14	M	W	28.5	4.48	0.66	38	850	Slight
8	14	M	W	28.4	4.50	0.63	33	735	Slight
9	16	M	W	28.7	4.13	0.68	59	1425	Slight
	Mean.....			28.6	4.37	0.66	43	1003	
10	21	M	W	27.4	4.32	1.17	90	2085	Slight
11	22	F	C	27.1	4.07	0.36	32	785	Slight
12	24	M	W	29.4	4.38	1.11	86	1970	Moderate
13	24	F	W	27.8	4.45	1.26	45	1010	Slight
14	25	F	W	27.7	4.80	0.68	23	480	Slight
15	27	M	C	27.4	4.09	0.98	41	1000	None
	Mean.....			27.8	4.35	0.93	53	1220	
16	31	M	W	25.1	3.80	0.80	34	895	Slight
17	32	F	W	27.5	3.28	1.20	65	1980	Slight
18	33	M	W	28.3	4.06	1.00	77	1896	Slight
19	33	M	C	28.0	4.83	1.07	85	1760	Slight
20	36	M	W	25.4	3.66	0.80	65	1775	None
21	37	F	W	28.7	3.10	0.76	17	550	None
22	39	M	W	25.3	3.61	1.12	47	1305	None
23	39	M	W	25.2	3.55	1.60	35	985	Moderate
	Mean.....			26.7	3.74	1.04	53	1390	
24	40	F	C	24.9	3.35	1.32	51	1525	Slight
25	43	M	C	24.3	3.21	1.05	173	5375	Slight
26	44	M	W	24.8	3.44	2.00	66	1920	Slight
27	44	M	W	24.8	3.44	2.00	50	1715	Moderate
28	45	F	W	24.1	3.51	1.10	23	655	None
29	45	F	C	27.4	3.89	0.96	52	1335	None
30	47	M	W	24.9	3.47	4.28	103	2960	Severe
31	47	M	W	22.4	3.40	1.34	126	3700	Slight
32	48	M	C	24.3	3.59	0.63	40	1115	None
33	49	M	W	25.3	3.13	1.02	52	1660	Slight
34	49	F	W	23.5	2.88	0.87	51	1770	Slight
35	49	F	C	24.4	3.25	2.17	99	3045	Moderate
	Mean			24.6	3.38	1.56	75	2230	
36	50	M	C	25.0	3.17	1.33	77	2430	Moderate
37	51	F	W	25.7	3.73	0.90	45	1205	Slight
38	52	M	W	24.6	3.47	1.19	112	3230	Moderate
39	52	M	W	24.0	3.39	2.18	74	2180	Moderate
40	52	M	W	23.8	2.56	1.09	131	5100	Moderate
41	52	M	C	29.3	3.88	1.88	88	2270	Slight

TABLE 1—Continued.

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	Glucuronidase Units/Gm. Wet Weight	Glucuronidase Units/Gm. Tissue N	Macroscopic-Arteriosclerosis
42	53	M	W	23.5	3.23	0.83	70	2170	Moderate
43	53	M	W	30.1	3.43	1.88	65	1890	Slight
44	53	F	W	24.2	3.26	1.10	88	2700	Slight
45	53	F	W	23.5	3.23	1.89	65	2010	Moderate
46	54	M	W	25.6	3.81	0.60	130	3410	Slight
47	54	M	W	26.0	3.37	1.68	86	2550	Moderate
48	55	M	W	27.0	3.68	1.40	78	2120	Slight
49	55	M	C	29.8	3.24	6.16	76	2340	Severe
50	56	M	W	26.8	3.88	3.71	17	440	Moderate
51	57	M	W	26.7	3.30	3.50	67	2030	Severe
52	57	M	W	24.2	3.21	2.54	41	1280	Moderate
53	57	F	W	26.4	3.37	1.14	37	1100	Slight
54	57	F	C	23.6	3.44	1.36	66	1980	Slight
55	58	M	W	23.8	3.20	1.76	110	3440	Moderate
56	58	M	W	29.8	2.51	8.70	163	6500	Severe
57	58	M	W	28.2	3.80	1.14	81	2130	None
58	58	F	W	25.1	3.42	2.12	49	1435	Severe
59	59	M	W	25.5	3.48	0.87	50	1440	None
	Mean.....			25.9	3.38	2.12	78	2390	
60	60	M	W	23.4	3.32	1.28	62	1870	Moderate
61	60	M	W	26.2	3.57	1.12	132	3690	Severe
62	60	M	W	23.5	3.21	3.53	59	1840	Severe
63	60	M	W	25.1	3.40	2.00	106	3110	Severe
64	61	M	W	28.3	2.72	4.19	119	4380	Severe
65	61	F	W	26.9	3.31	1.04	61	1840	None
66	62	M	W	29.4	3.72	2.95	114	3060	Moderate
67	62	F	W	27.3	2.84	3.95	137	4820	Severe
68	63	M	W	27.2	3.45	2.40	32	930	Moderate
69	63	M	W	26.9	3.21	4.95	61	1900	Severe
70	64	M	W	26.1	3.33	3.57	119	3560	Moderate
71	64	M	W	26.4	3.34	3.12	104	3120	Moderate
72	64	M	W	26.5	3.28	2.23	176	5350	Moderate
73	64	M	C	24.8	3.26	2.38	47	1440	Slight
74	65	M	W	24.4	3.26	2.24	71	2180	Moderate
75	65	M	W	25.4	3.02	4.46	115	3810	Severe
76	65	M	W	23.2	3.16	0.99	51	1620	Slight
77	65	M	C	25.7	3.47	1.44	76	2195	Moderate
78	68	M	W	24.4	3.25	1.88	50	1535	Moderate
79	69	M	W	25.1	3.54	1.75	153	4310	Moderate
80	69	M	C	25.3	3.13	2.74	64	2040	Severe
	Mean.....			25.8	3.27	2.58	91	2790	
81	70	M	W	24.7	3.42	1.87	51	1490	Moderate
82	70	M	C	25.9	3.51	1.62	38	1085	Slight
83	71	M	W	28.0	3.24	0.69	129	3980	Moderate
84	72	M	W	27.7	3.28	2.50	88	2680	Severe
85	72	M	W	26.4	3.27	3.45	67	2050	Severe
86	72	M	W	30.0	3.94	2.82	83	2110	Severe
87	72	F	W	23.3	2.93	2.40	62	2115	Severe
88	73	M	W	27.4	3.28	1.80	59	1800	Moderate
89	73	F	W	24.1	3.30	2.30	82	2480	Severe
90	74	M	C	27.2	3.56	1.51	33	925	Moderate
91	74	F	C	26.6	3.39	2.30	61	1800	Severe

TABLE 1—Continued.

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	Glucuronidase Units/Gm. Wet Weight	Glucuronidase Units/Gm. Tissue N	Macroscopic-Arteriosclerosis
92	75	M	W	29.8	2.98	4.38	55	1845	Severe
93	75	M	C	24.1	3.33	0.72	77	2310	Slight
94	77	F	W	37.2	2.62	3.68	95	3630	Severe
95	79	F	W	25.7	3.29	2.03	86	2610	Severe
	Mean.....			27.2	3.28	2.44	71	2190	
96	82	M	W	30.1	3.78	2.62	40	1060	Slight
97	87	M	W	28.3	3.31	2.46	99	2990	Severe
98	87	F	W	25.0	3.50	1.55	38	1085	Severe
99	88	M	W	23.0	2.70	1.20	85	3145	Moderate
100	88	F	W	28.2	3.29	4.60	15	455	Severe
	Mean.....			26.9	3.32	2.49	55	1745	
	Grand Mean....			26.4	3.53	1 91	71	2103	

TABLE 2. GLUCURONIDASE ACTIVITY OF 44 SAMPLES OF HUMAN PULMONARY ARTERY.

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	Glucuronidase Units/Gm. Wet Weight	Glucuronidase Units/Gm. Tissue N	Macroscopic Arteriosclerosis
2	0.5	M	C				97		None
3	1.5	F	W				15		None
	Mean.....						56		
7	14	M	W	27.7	4.05		66	1630	None
8	14	M	W	29.3	4.58		58	1265	None
	Mean.....			28.5	4.32		62	1448	
10	21	M	W	25.0	4.02	0.52	46	1145	None
11	22	F	C				59		Slight
13	24	F	W	26.5	4.15	0.87	54	1300	None
14	25	F	W				35		None
	Mean.....			25.8	4.09	0.70	49	1223	
16	31	M	W	20.9	3.02	0.71	29	960	None
17	32	F	W	29.2	4.90		73	1490	None
21	37	F	W	26.0	3.80		41	1080	None
	Mean.....			25.4	3.92	0.71	48	1176	
24	40	F	C	27.6	3.57	2.32	40	1120	None
25	43	M	C			0.93	69		Slight
31	47	M	W	25.3	3.84		63	1640	Slight
35	49	F	C	24.6	5.85	1.84	73	1245	Slight
	Mean.....			24.8	4.31	1.69	61	1335	
40	52	M	W	21.3	3.06	0.94	244	8000	Slight
41	52	M	C	26.1	3.67	0.81	122	3320	None

TABLE 2—Continued.

No.	Age (Years)	Sex	Race	Dry Matter, %	Nitrogen, % of Wet Weight	Cholesterol, % of Wet Weight	Glucuronidase Units/Gm. Wet Weight	Glucuronidase Units/Gm. Tissue N	Macroscopic-Arteriosclerosis
43	53	M	W	27.2	3.85	1.22	41	1065	None
44	53	F	W	23.2	3.57	0.80	104	2830	None
45	53	F	W	23.2	3.39	0.81	73	2155	Slight
48	55	M	W	26.0	3.56	0.78	75	2110	None
49	55	M	C	23.3	3.50	2.50	70	2000	Slight
50	56	M	W	21.9	3.37	2.85	172	5110	Slight
54	57	F	C	21.5	2.95	2.05	73	2470	Slight
56	58	M	W	21.6	3.00	2.50	143	4770	Moderate
57	58	M	W	24.3	3.41	0.92	96	2815	None
	Mean.....			23.6	3.39	1.47	110	3330	
63	60	M	W	21.1	2.91	1.80	178	6110	Slight
66	62	M	W	26.6	3.70	1.08	81	2190	Slight
67	62	F	W	22.4	3.29	1.75	90	2735	None
69	63	M	W	23.9	3.62	1.84	93	2570	Slight
71	64	M	W	21.6	3.13	1.32	102	3260	Slight
72	64	M	W	23.9	3.20	1.27	136	4250	Slight
75	65	M	W	30.8	4.38	1.20	88	2010	None
78	68	M	W	23.2		0.96	63		Slight
79	69	M	W	38.7	5.60	1.49	84	1500	Slight
	Mean.....			25.8	3.79	1.42	102	3090	
81	70	M	W	21.2	2.96	1.75	125	4230	Slight
83	71	M	W	23.2	2.86		104	3630	Slight
86	72	M	W	20.0	2.69	1.15	83	3085	Slight
94	77	F	W	20.9	2.88	0.54	63	2185	Moderate
95	79	F	W	24.8	3.26	1.19	59	1810	Slight
	Mean.....			22.0	2.93	1.15	87	2990	
96	82	M	W	20.7	3.57	1.60	69	1935	Slight
97	87	M	W	21.2	3.17	0.75	93	2930	None
98	87	F	W				22		Slight
99	88	M	W	20.0	2.92	3.18	69	2360	Slight
	Mean.....			20.6	3.22	1.84	63	2410	
	Grand Mean....			24 3	3 64	1.34	83	2516	

The average glucuronidase activity observed for the 100 aortic samples was 71 units/Gm. wet tissue, and for the 44 pulmonary artery samples 83 units/Gm. wet tissue.

An analysis of the glucuronidase values reveals that the enzyme activity of the arterial samples derived from the women in general was lower than the activity found in the samples from the men. Thus the average activity of the aortic samples from the women was only 62 per cent, and of the pulmonary artery samples 80 per cent of the glucuronidase values observed for the men in the corresponding age groups. If only the samples from the

TABLE 3. MEAN BETA-GLUCURONIDASE ACTIVITY OF HUMAN AORTIC AND PULMONARY ARTERY SAMPLES IN VARIOUS DECADES.

Age Group (Years)	Aorta			Pulmonary Artery		
	Number of Samples	Mean Glucuronidase Activity		Number of Samples	Mean Glucuronidase Activity	
		Units/Gm. Wet Tissue	Units/Gm. Tissue N		Units/Gm. Wet Tissue	Units/Gm. Tissue N
0– 9	6	29	770	2	56	
10–19	3	43	1003	2	62	1448
20–29	6	53	1220	4	49	1223
30–39	8	53	1390	3	48	1176
40–49	12	75	2230	4	61	1335
50–59	24	78	2390	11	110	3330
60–69	21	91	2790	9	102	3090
70–79	15	71	2190	5	87	2990
80–88	5	55	1745	4	63	2410
	Mean	71	2103	Mean	83	2516

white subjects are considered, percentage values of 60 and 88, respectively, are found.

The mean glucuronidase values observed for the various decades are listed in table 3. It will be seen from the data that a definite tendency was noted for the enzyme activity to increase till the age of 50–69 years, after which a decrease in the mean glucuronidase values was noted. The enzyme activity values calculated on the basis of the tissue nitrogen content in general showed the same variation with age as the values expressed per unit of wet tissue weight.

TABLE 4. CORRELATION BETWEEN DEGREE OF ARTERIOSCLEROSIS OF HUMAN AORTIC AND PULMONARY ARTERY SAMPLES FOR INDIVIDUALS AGED 50-79 YEARS AND GLUCURONIDASE ACTIVITY OF TISSUE.

Degree of Macroscopic Arteriosclerosis	Number of Samples	Average Cholesterol Content of Tissue % of Wet Weight	Mean Glucuronidase Units/Gm. Wet Tissue
Aorta			
None	4	1.17	58
Slight	11	1.31	68
Moderate	24	1.95	84
Severe	21	3.38	87
Pulmonary Artery			
None	7	1.04	85
Slight	15	1.53	109
Moderate	2	1.52	103

TABLE 5. BETA-GLUCURONIDASE ACTIVITY OF 16 SAMPLES OF HUMAN CORONARY ARTERY FROM CHILDREN AND YOUNG ADULTS.

No.	Age (Years)	Sex	Race	Glucuronidase Units/Gm. Wet Tissue	
				Coronary Artery	Aorta
4	3	M	W	13	2
5	3	M	W	25	42
7	14	M	W	89	38
8	14	M	W	78	33
9	16	M	W	43	59
10	21	M	W	114	90
11	22	F	W	26	32
12	24	M	W	56	86
13	24	F	W	54	45
14	25	F	W	37	23
16	31	M	W	59	34
17	32	F	W	80	65
18	33	M	W	30	97
19	33	M	C	52	85
21	37	F	W	47	17
22	39	M	W	78	47
Mean				55	50

The relationship between the age of the subjects and the glucuronidase activity of the aortic samples is presented graphically in figure 1.

In order to evaluate the glucuronidase values for the 50-79 year old subjects in greater detail, an analysis was made of the relationship between the macroscopic grading of the degree of arteriosclerosis present in the samples and the enzyme activities found. The results of this study are presented in table 4.

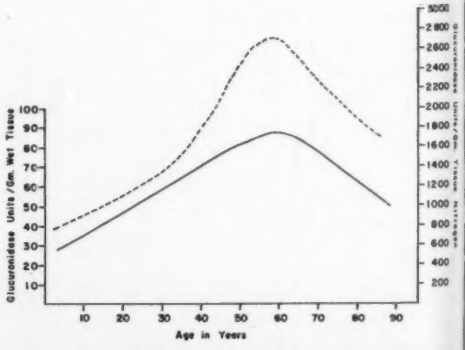

Fig. 1. Smoothed curves indicating variation with age in glucuronidase activity of human aortic tissue. Solid curve = glucuronidase units/Gm. wet tissue. Dashed curve = glucuronidase units/Gm. tissue nitrogen.

It will be seen from the data listed in the table that a tendency was observed for the glucuronidase activity to increase with the degree of arteriosclerosis present. It will further be noted that a good agreement was found between the macroscopic evaluation of the samples and the cholesterol tissue values. A calculation for the aortic samples of the coefficient of correlation between the tissue cholesterol content and the glucuronidase values for the age range 50-79 years showed an r value of +0.26 ($t = 2.06$, $N = 60$). For the corresponding pulmonary artery samples the coefficient of correlation : Cholesterol content / glucuronidase activity was +0.23 ($t = 1.10$, $N = 24$).

Coronary Artery System.—The results of the glucuronidase measurements in 16 samples of the coronary artery from children and young adults are shown in table 5. For comparison the enzyme activities observed for the aortic samples from the same subjects have also been listed in the table. The average glucuronidase value found for the coronary artery system of this group of subjects was 55 units / Gm. wet tissue, as compared with 50 units / Gm. wet tissue for the aortic samples from the same individuals.

DISCUSSION

The investigation has established the presence of a definite beta-glucuronidase activity in the tissue of the human aorta, pulmonary artery, and coronary artery system. The average glucuronidase values for the arterial tissue found in the present study are 50 to 100 times higher than the glucuronidase units of human plasma, reported by Fishman, Springer, and Brunetti (2). In comparison with the glucuronidase activity of human parenchymatous organs (5) the enzyme values observed for arterial tissue are quite low, namely about 0.5 per cent of the activity reported for liver tissue, and 1 per cent of that found in the spleen and kidney.

The role of beta-glucuronidase in various tissues, including the relation, if any, of the enzyme to glucuronide synthesis, is still not clarified (1). A valid discussion of the correlation observed in the present study between the degree of arteriosclerotic changes in the vessels and the tissue glucuronidase activity is therefore not possible at the present stage.

SUMMARY

Determinations were made of the beta-glucuronidase activity of 100 samples of the human thoracic aorta and 44 samples of the pulmonary artery. The age of the individuals from whom the samples were derived ranged between 3 days and 88 years. The analyses were performed by the procedure of Talalay, Fishman, and Huggins. The average glucuronidase activity observed for the aortic samples was 71 units / Gm. wet tissue, and for the pulmonary artery samples 83 units /Gm. wet tissue. A tendency was noted for the enzyme activity to increase till the age of 50-69 years, after which a decrease occurred.

The mean glucuronidase activity of 16 samples of the coronary artery system derived from subjects aged 3 to 39 years was 55 units / Gm. wet tissue, as compared with 50 units /Gm. wet tissue for the aortic samples from the same subjects.

The correlation between the degree of arteriosclerosis present in the arterial samples and the observed glucuronidase value is analyzed.

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AGING AND PUPILLARY RESPONSE TO LIGHT AND SOUND STIMULI

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IN A PREVIOUS article (2) the results of a study employing pupillography on psychosensory restitution and aging indicated; (a) statistically significant differences in the pupillary response to light and sound stimuli occurred with increasing age as reflected in decrease in mean maxima and minima pupil diameters, extent of constriction, and response velocity; and (b) the relationship between age and the pupillary phenomena was significant, substantial, linear, and negative.

The present article is concerned with increasing age and (a) the rate of change in pupillary response to light and sound stimuli; (b) the velocity of the pupillary response to light and sound stimuli during parts of the total process of constriction; and (c) the relative control of the iris over the amount of light striking the retina during the response to light and sound stimuli.

MATERIAL AND METHOD

Cinephotography utilizing infrared illumination was employed to record the size of the pupil as it alternately constricted and dilated in response to light stimuli (12.2 ft-c.) of one second duration presented every four seconds. After 60 light stimuli, when the mobility of the pupil was lessened and the responses reduced, a sound stimulus (97 db.) was presented which restored pupillary functioning. The apparatus used and the procedure followed have been described elsewhere (2).

Data were obtained (2) for 94 ostensibly normal, white subjects between the ages of 7.5 and 90.8 years without known influencing pathologic conditions. They were selected by means of interviews, and neurologic and ophthalmologic examinations.

RESULTS AND DISCUSSION

In order to evaluate the rate of change in pupillary response to light and sound stimuli which may be attributed to increasing age, the relation between age and pupillary response was tested for deviation from linear regression employing the *F* test (3). In no instance was there a significant deviation from linear regression. Therefore, the value of the slope constant *(b)* of the linear regressions was determined, and regression equations of the straight line function, $\bar{Y}=\overline{Y}+byx(X-\overline{X})$, were fitted by the method of least squares to the data. The slope constant values obtained and their standard errors are presented in table 1. All slopes describing the relationship under investigation were found to be negative and differed statistically from zero (table 1). Figure 1 is a graphic presentation of the plots of the curves and of the means for the pupillary responses.

The slope differences were tested for significance employing the *F* test. Significant differences between slope values were found for pupil size at onset of light and at minimum size ($F=6.98$, with 1 and 180 *df*, $p<.01$; $F=6.48$, with 1 and 180 *df*, $p<.05$; $F=4.97$, with 1 and 182 *df*, $p<.05$ for the initial, fatigued,* and restituted† responses, respectively). Among the pupillary conditions, a significant difference was found only between the slope values for the initial and restituted responses for extent of response ($F=5.16$, with 1 and 181 *df*, $p<.05$). The difference between the slope values for the initial and fatigued responses for this category, however, was close to significance at the .05 per cent level.

Although the relationship between age and pupil size was found to be linear for the

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Some of the data reported in this article were presented before the 1952 meeting of the American Psychological Association, Washington, D. C.

*Fatigue is defined, for the purposes of this experiment, as the reduction of pupillary functioning, after prolonged light stimulation, which is shown in the lessened mobility of the pupil and in smaller pupillary responses.

†Restitution is defined as the reconstitution of the pupillary response.

TABLE 1. VALUES OF SLOPE CONSTANT, *b*, FOR THE REGRESSION OF PUPILLARY RESPONSES ON AGE.

Item	Initial		Fatigued		Restituted	
	b	Standard Error	*b*	Standard Error	*b*	Standard Error
Size at Onset of Light	−.0331***	±.0041	−.0254***	±.0028	−.0284***	±.0026
Size at Minimum	−.0194***	±.0030	−.0161***	±.0020	−.0200***	±.0024
Extent of Constriction	−.0137***	±.0020	−.0093***	±.0014	−.0083***	±.0010
Speed of Constriction	−.0075***	±.0014	−.0103***	±.0016	−.0115***	±.0019
Speed for 4th Tenth Sec.	−.0025***	±.0006	−.0039***	±.0006	−.0039***	±.0006
Speed for 6th Tenth Sec.	−.0022***	±.0004	−.0010**	±.0003	−.0010*	±.0004

*Significant at .05 level.
**Significant at .01 level.
***Significant at .001 level.
N = 94 (47 male, 47 female).

TABLE 2. ANALYSIS OF VARIANCE OF THE DATA ON SPEED OF PUPILLARY CONSTRICTION FOR THE FOUR AGE GROUPS.[a]

Item	Source of Variation	MS	*df*		*F*
Speed during Fourth Tenth Second	Between age groups	.65[b]	3		15.70***
	Between Ss in same group	.04	86		
	Total between Ss			89	
	Between responses	.36	2		44.44***
	Responses × age groups	.008	6		1.03
	Pooled Ss × responses	.008	164		
	Total within Ss			172	
	Total			261	
Speed during Sixth Tenth Second	Between age groups	.10	3		6.78***
	Between Ss in same group	.01	86		
	Total between Ss			89	
	Between responses	.11	2		25.06***
	Responses × age groups	.01	6		2.28*
	Pooled Ss × responses	.004	164		
	Total within Ss			172	
	Total			261	

[a]Bartlett test for homogeneity of variance: values obtained not significant with the exception of Fatigue during Fourth Tenth Sec. < .05.
[b]Computations were made with 5 decimal places so rounding discrepancies will be found if only 2 are used.
*$p < .05$
***$p < .001$

normal subjects in this study, it is logical to assume that somewhere on the age slope the relationship becomes curvilinear, since the pupil never has a zero diameter. A curvilinear relationship might have become apparent in this study if there had been more subjects over 90 years of age. Moreover, increased fatigue and restitution, as well as abnormal and pathologic conditions, may cause the relationship to become curvilinear

anywhere on the age slope. Although the rate of change in pupillary response under certain conditions may afford a valuable diagnostic sign, it may also act as an influencing variable in some visual studies.

In order to evaluate the velocity of the pupillary response to light and sound stimuli during parts of the total process of constriction, the amount of constriction or dilation in terms of 0.01 mm. within each successive 0.1 sec. for the initial, fatigued, and restituted responses was determined (fig. 2). Inspection of figure 2 suggests that (a) age differences in velocity decrease following the period of peak velocity during the constriction; and (b) conditions of fatigue and restitution affect the velocity of response dissimilarly in various parts of the total process of constriction.

Therefore, the velocity during the fourth 0.1 sec. and the velocity during the sixth 0.1 sec. of constriction were selected for further analysis. The fourth 0.1 sec. represents the period during which the peak velocity occurred, and the sixth 0.1 sec. the period during which a noticeable decrease in velocity was evident. A decrease in the velocity of the pupillary response during the fourth 0.1 sec. of constriction with increasing age is suggested by an inspection of figure 3 and is confirmed by the statistical analyses of the

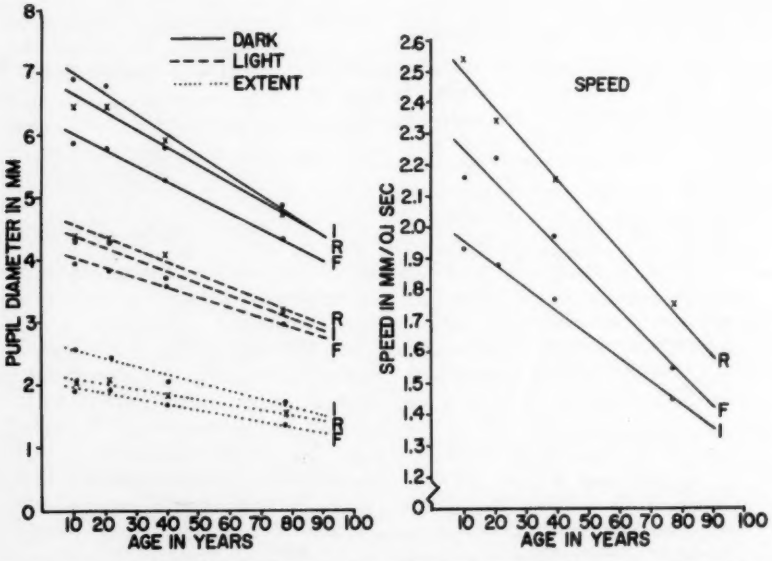

FIG. 1. Relation between age and pupillary response as shown in grouping the regression lines for pupil diameter at onset of light (Dark); pupil diameter at minimum size (Light); extent and speed of constriction. I, initial or rested pupil; F, fatigued pupil; R, restituted pupil.

The straight line regression equation was fitted to these data and the values of its constants a and b are as follows:

Dark: I, $\tilde{Y} = -.03309X + 7.33$; F, $\tilde{Y} = -.02539X + 6.27$;
R, $\tilde{Y} = -.02835X + 6.93$

Light: I, $\tilde{Y} = -.01938X + 4.59$; F, $\tilde{Y} = -.01610X + 4.20$;
R, $\tilde{Y} = -.02003X + 4.75$

Extent: I, $\tilde{Y} = -.01370X + 2.73$; F, $\tilde{Y} = -.00928X + 2.07$;
R, $\tilde{Y} = -.00832X + 2.18$

Speed: I, $\tilde{Y} = -.00751X + 2.03$; F, $\tilde{Y} = -.01030X + 2.36$;
R, $\tilde{Y} = -.01147X + 2.62$

data (tables 2 and 3). During the sixth 0.1 sec. of constriction a significant decrease in velocity with increasing age is found in the initial response only.

Analysis of variance of the data for velocity during this period for the fatigued and restituted responses reveals no significant F values, indicating that the significant F value in table 2 is produced by the significant difference between pairs of means in the initial response only (tables 2 and 3). The effect of the conditions of fatigue and restitution on the velocity of response during the sixth 0.1 sec. produces a different arrangement from that in the fourth 0.1 sec., for a reversal takes place for fatigue and restitution (fig. 3). The slope differences (fig. 4) were tested for significance (F test). No significant difference was found between the various pairs of slope values for the fourth 0.1 sec. of constriction. A significant difference (F=5.52, with 1 and 169 df, p<.05) was found, however, between the slope values for the initial and fatigued, and for the initial and restituted responses in the sixth 0.1 sec. of constriction (F=4.48, with 1 and 171 df, p<.05).

Abnormal and pathologic conditions may produce significant changes in the pupillary response during various periods of the total constriction; thus analyses of the response during certain periods of the total constriction may be valuable for diagnostic purposes.

A significant, linear, and negative relationship was found between age and the velocity of response during the two periods of constriction evaluated. The product-moment coefficients for the correlation between age and the fourth 0.1 sec. are −.42, −.57, and

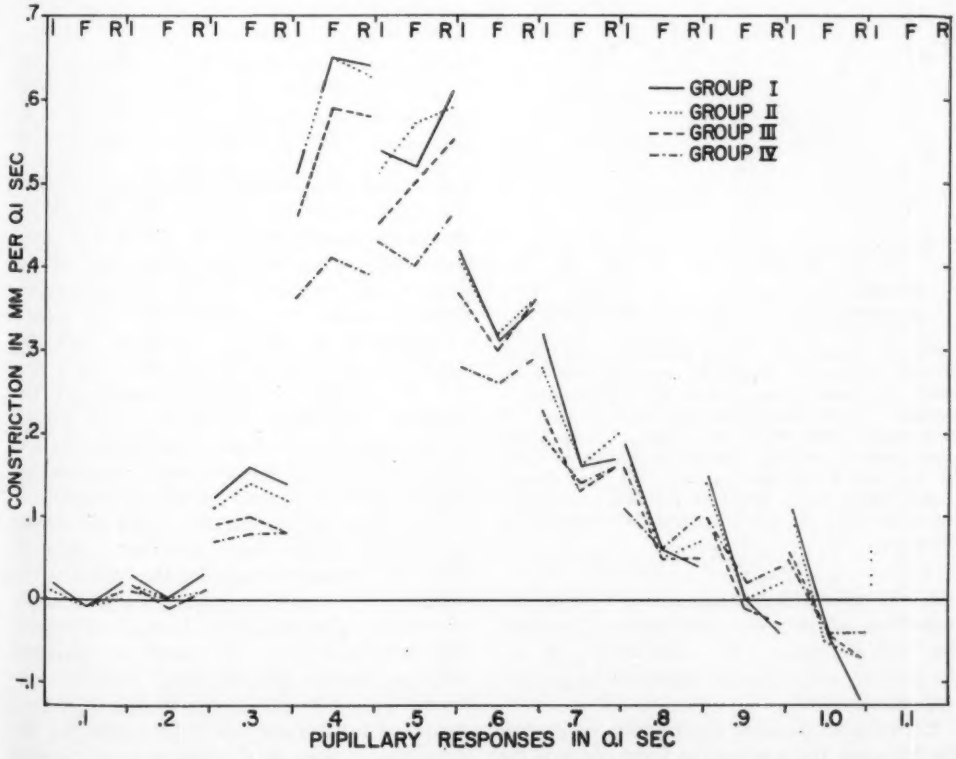

FIG. 2. Mean speed of pupillary constriction during each successive tenth of a second within the 4 age groups for the initial (I), fatigued (F), and restituted (R) responses. Rulings below zero indicate dilatation. I, 7.5 to 15.0 years; II, 18.1 to 28.2 years; III, 30.5 to 52.7 years; IV, 70.4 to 90.8 years.

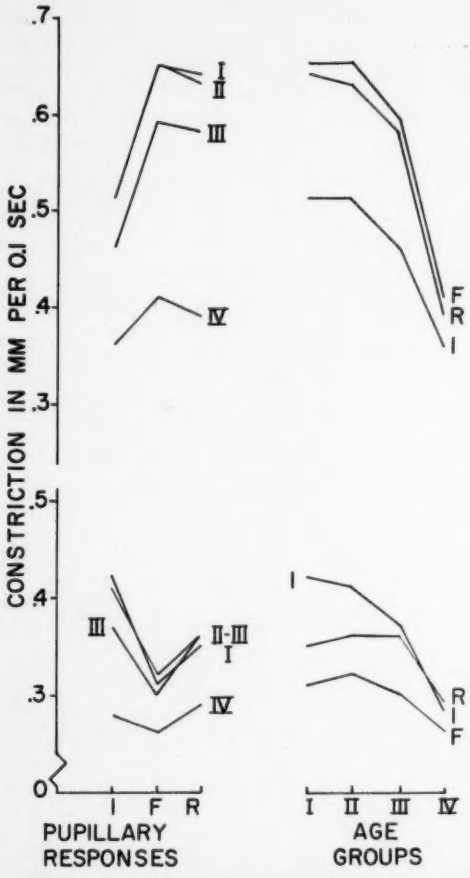

FIG. 3. Upper left: Mean speed of pupillary constriction during the fourth 0.1 sec. of constriction within the 4 age groups. Lower left: Mean speed of pupillary constriction during the sixth 0.1 sec. of constriction within the 4 age groups. Upper right: Mean speed of pupillary constriction during the fourth 0.1 sec. of constriction between the age groups. Lower right: Mean speed of pupillary constriction during the sixth 0.1 sec. of constriction between the age groups.

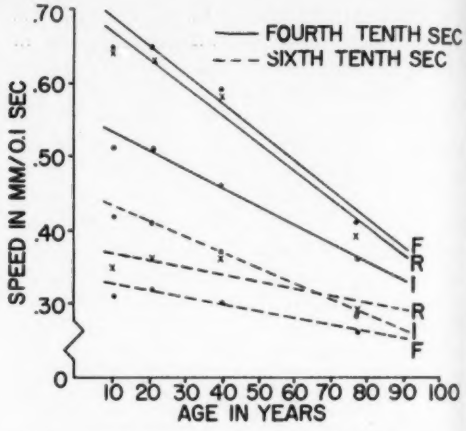

FIG. 4. Relation between age and pupillary response as shown in grouping the regression lines for speed of response during the fourth and the sixth 0.1 sec. of pupillary constriction.

The straight line regression equation was fitted to these data and the values of its constants a and b are as follows:

Speed during fourth 0.1 sec: I, $\tilde{Y} = -.00248X + .56$;
F, $\tilde{Y} = -.00392X + .73$; R, $\tilde{Y} = -.00389X + .71$
Speed during sixth 0.1 sec: I, $\tilde{Y} = -.00219X + .46$;
F, $\tilde{Y} = -.00097X + .34$; R, $\tilde{Y} = -.00101X + .38$

−.59 for the initial, fatigued, and restituted responses, respectively; and between age and the sixth 0.1 sec. −.53, −.32, and −.26 for the initial, fatigued, and restituted responses, respectively.

In order to evaluate the relative control of the iris over the amount of light striking the retina, the constriction of the pupil in relation to original diameter in the response to light and sound stimuli was investigated employing the formula D^2-L^2/D^2. The results are shown graphically in fig. 5. Table 4 presents the results of an analysis of variance of the data which revealed (a) no significant differences among the means of the age groups as indicated by the low F value, and (b) significant differences (F=41.46, with 2 and 175 df, $p<.001$) among the means of the pupillary conditions (I, F, R). The results of the application of the t technique to test the significance of the difference between the various pairs of means are shown in table 5.

The behavior of the iris with increasing age found in this study was not consistent with expectations because of the fact that the older iris is characterized by vascular sclerosis and hyaline degeneration. Birren, Casperson, and Botwinick (1) also noted an apparent constant relative constriction. Important to certain visual studies is the finding that conditions of fatigue and restitution influence the governing power of the iris over the mount of light striking the retina (fig. 5 and table 5).

TABLE 3. THE DIFFERENCES[a] BETWEEN THE MEANS OF THE PUPILLARY SPEED DURING FOURTH AND SIXTH TENTH SECOND.

Age Groups[b]	Pupillary Responses	*df*	Speed During Fourth Tenth Sec.		Speed During Sixth Tenth Sec.	
			Difference	Level of Significance	Difference	Level of Significance
I—II			0.00		0.01	
I—III			0.05		0 05	
I—IV	Initial	86	0.15	*	0.14	**
II—III			0.05		0.04	
II—IV			0.15	*	0.13	**
III—IV			0.10		0.09	
I— II			0.00		−0.01	
I—III			0.06		0.01	
I—IV	Fatigued	86	0.24	**	0.05	
II—III			0.06		0.02	
II—IV			0.24	**	0.06	
III—IV			0.18	**	0.04	
I— II			0.01		−0.01	
I—III			0.06		−0.01	
I—IV	Restituted	86	0.25	**	0.06	
II—III			0.05		0.00	
II—IV			0.24	**	0.07	
III—IV			0.19	**	0.07	
	I—F		−0.05		0.02	
IV	I—R	164	−0.03		−0.01	
	F—R		0.02		−0.03	
	I—F		−0.13	**	0.07	**
III	I—R	164	−0.12	**	0.01	
	F—R		0.01		−0.06	**
	I—F		−0.14	**	0.09	**
II	I—R	164	−0.12	**	0.05	**
	F—R		0.02		−0.04	*
	I—F		−0.14	**	0.11	**
I	I—R	164	−0.13	**	0.07	**
	F—R		0.01		−0.04	

[a]Speed in .01 mm. per .1 sec.
[b]N = 23 in Group IV; 24 in Group III; 24 in Group II; 19 in Group I.
*Significant at the .05 level.
**Significant at the .01 level.

TABLE 4. ANALYSIS OF VARIANCE OF THE DATA ON THE RATIO OF THE DIFFERENCE BETWEEN PUPIL DIAMETERS FOR THE 4 AGE GROUPS.[a]

Item	Source of Variation	MS	*df*	*F*
	Between age groups	.01	3	.90
	Between Ss in same group	.01	90	
	Total between Ss		93	
D^2-L^2/D^2	Between responses	.08	2	41.46***
	Responses × age groups	.003	6	1.62
	Pooled Ss × responses	.002	175	
	Total within Ss		183	
	Total		276	

[a]Computations were made with 5 decimal places so rounding discrepancies will be found if only 2 are used.
***$p < .001$.

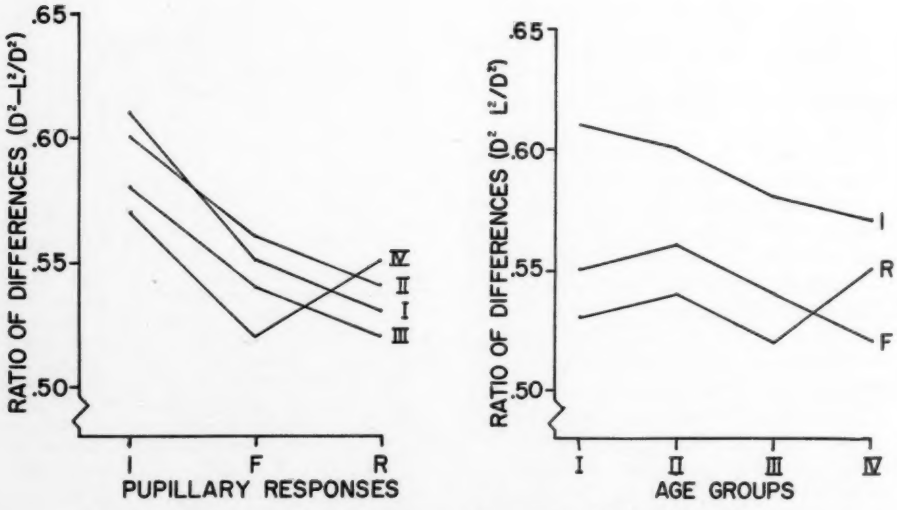

FIG. 5. Relative control of the iris over the amount of light striking the retina.

TABLE 5. THE DIFFERENCES BETWEEN THE MEANS OF D^2-L^2/D^2 WITHIN THE 4 AGE GROUPS.

Age Groups	Pupillary Responses	*df*	Difference	Level of Significance
IV	I—F	175	0.05	**
	I—R		0.02	a
	F—R		−0.03	*
III	I—F	175	0.04	**
	I—R		0.06	**
	F—R		0.02	a
II	I—F	175	0.04	**
	I—R		0.06	**
	F—R		0.02	a
I	I—F	175	0.06	**
	I—R		0.08	**
	F—R		0.02	a

*Significant at the .05 level.
**Significant at the .01 level.
aSignificant (borderline) at the .05 level.

SUMMARY

The following conclusions may be drawn from the results of this pupillographic study on pupillary response to light and sound stimuli:

1. No significant difference in rate of change occurs with age in mean maxima and minima diameters, extent of constriction, and response velocity as revealed by the tests of deviation from linear regression.

2. Significant differences were found between slope values for pupil size at onset of light stimulus and at minimum constriction, and between the initial and restituted responses for extent of constriction.

3. Age, as well as fatigue and restitution, affects the velocity of pupillary response to light and sound stimuli dissimilarly in parts (0.1 sec.) of the total process of constriction.

4. A significant, linear, and negative relationship was found between age and the velocity of pupillary response during the fourth 0.1 sec. of constriction, and between age and the velocity of the response during the sixth 0.1 sec. of constriction.

5. Age did not affect the relative control of the iris over the amount of light striking the retina, for the older pupil, in proportion to initial size, constricted as much as the young. Conditions of fatigue and restitution, however, did influence this relative control.

6. Age; states of stress, tension, and fatigue; various drugs; certain abnormal and pathologic conditions; and parasympathetic-sympathetic relationship are among the variables which merit consideration in visual studies, especially those relating to the condition of the eye as a diagnostic tool.

7. The older eye apparently does not react as feebly as is generally assumed. Further studies on the pupillary response to light and sound stimuli in relation to aging are indicated. The author is continuing analyses of the statistical data of this study in relation to aging.

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AGING AND DECAY OF PUPILLARY PSYCHOSENSORY RESTITUTION*

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IN A PREVIOUS article (1) the results of a study employing pupillography on aging and pupillary psychosensory restitution (PPR)† were presented which indicated (a) statistically significant differences in the PPR occurring with increasing age as reflected in a progressive decrease in mean maxima and minima pupil diameters, extent of constriction, and response velocity; and (b) a substantial, significant, linear, and negative relationship between age and the PPR. Evaluation of the decay of the PPR may be a valuable contribution to studies on aging. The purpose of this article is to present the results of a study of the decay of the PPR in relation to aging.

MATERIAL AND METHOD

The apparatus used and the procedure followed have been described elsewhere (1). Data on pupil size, extent of constriction, and response velocity were obtained (1) for 94 white male and female subjects between the ages of 7.5 and 90.8 years without known influencing pathologic conditions.

RESULTS AND DISCUSSION

The results of the experiment are summarized in tables 1 and 2. Figures 1 and 2 present the results on the PPR and decay of the PPR‡ graphically. Inspection of the tables and figures suggests that (a) pupil size, extent of constriction, and response velocity during decay of the PPR decreased with increasing age, and (b), in general, variability of response increased with age. The indication (a) above is supported by analysis of variance results (F values range from 8.93 to 30.77, with 3 and 87 df, $p < .001$). The significance of the value of F may be attributed to the differences in the means as Bartlett's test indicated that the variances did not differ significantly. Since there were significant differences among age groups in all categories, t tests were performed to test the significance of the differences between pairs of means among the groups, and between PPR and decay of the PPR (table 3). Decay of PPR was greater in dilation than in constriction for the 4 age groups; and greater in the middle age range than in the youngest and the oldest age ranges. Further studies on the phenomenon of decay of the PPR are indicated for it evidences promise of being a sensitive and discriminative measure.

The relationship between age and decay of the PPR was found to be significant, linear, and negative, the product-moment correlation coefficients for the correlations being −.72 for pupil size at onset of light, −.63 for pupil size at minimum constriction, −.51 for extent of constriction, and −.49 for response velocity.

In order to determine the rate of change in pupillary response to light and sound stimuli during decay of the PPR which may be attributed to increasing age, the relation between age and pupillary response during decay of PPR was tested for deviation from linear regression employing the F test (2). No significant deviation from linear regression was found. Figure 3 is a graphic presentation of the curves and of the means of pupillary response during decay of the PPR. The assumption that pupil size is a linear function of age is not tenable, however, since the pupil never has a zero diameter. Increased age and pathologic conditions may induce curvilinearity.

SUMMARY

The results of a study of decay of the pupillary psychosensory restitution (PPR) based on data obtained by means of pupil-

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This article is based upon a dissertation submitted to the Graduate School of Fordham University in partial fulfillment of the requirements for the Ph. D. degree. The writer is indebted to Dr. Henryk Misiak, who directed the research, and to Dr. Otto Lowenstein, Director of the Laboratory of Pupillography, Institute of Ophthalmology, Columbia-Presbyterian Medical Center, New York, where the experimental work was done.

†PPR is defined as reconstitution of pupillary response following pupillary fatigue.

‡Determined from measurements of the 60-second response to light stimulation.

lography for 94 apparently normal subjects between the ages of 7.5 and 90.8 years revealed that decay of the PPR is greater in pupillary dilation than in constriction for all age groups; and greater for the middle age range (18 to 50 years) than for the youngest and the oldest age groups. Decay of the PPR may provide a useful and differential aid in analyses in gerontologic studies. Changes in parasympathetic-sympathetic relationship seem to be reflected in this phenomenon.

Table 1. PUPIL SIZE, EXTENT AND SPEED OF PUPILLARY CONSTRICTION FOR THE FOUR AGE GROUPS.[a]

Age[b] Group	Pupillary Response	Size at Onset of Light: Mean Diameter	SD	Range from	Range to	Mean Log Area	Size at Minimum Constriction: Mean Diameter	SD	Range from	Range to	Mean Log Area
IV	Initial	4.87	1.37	2.76	8.08	1.27	3.15	0.88	2.01	5.04	0.89
	Fatigued	4.32	0.83	2.54	6.16	1.17	2.96	0.47	1.91	3.92	0.84
	Restituted	4.71	0.80	3.05	6.30	1.24	3.15	0.56	2.02	4.10	0.89
	Decayed	4.54	0.81	3.10	6.29	1.21	3.08	0.50	2.02	4.14	0.87
III	Initial	5.78	1.03	4.00	7.94	1.42	3.71	0.73	2.79	5.72	1.03
	Fatigued	5.28	0.81	3.94	7.04	1.34	3.59	0.63	2.42	4.89	1.01
	Restituted	5.91	0.74	4.64	7.50	1.44	4.09	0.71	3.08	6.00	1.12
	Decayed	5.62	0.80	4.37	7.55	1.39	3.82	0.71	2.67	5.87	1.06
II	Initial	6.77	0.90	5.35	8.58	1.56	4.29	0.78	3.15	6.06	1.16
	Fatigued	5.79	0.69	4.42	7.04	1.42	3.85	0.62	2.69	4.96	1.07
	Restituted	6.42	0.60	5.19	7.53	1.51	4.34	0.70	3.12	5.64	1.17
	Decayed	6.19	0.65	5.28	7.38	1.48	4.20	0.73	2.90	5.53	1.14
I	Initial	6.88	0.80	5.73	8.36	1.57	4.29	0.62	3.50	5.64	1.16
	Fatigued	5.86	0.62	4.70	6.70	1.43	3.95	0.50	3.20	4.64	1.09
	Restituted	6.42	0.53	5.34	7.54	1.51	4.38	0.60	3.31	5.16	1.18
	Decayed	6.18	0.56	5.40	6.91	1.48	4.24	0.46	3.43	4.92	1.15

		Extent of Pupillary Constriction: Mean Extent	SD	Range from	Range to	Speed of Pupillary Constriction: Mean Speed	SD	Range from	Range to
IV	Initial	1.72	0.60	0.54	3.04	1.44	0.41	0.54	2.19
	Fatigued	1.36	0.46	0.48	2.44	1.54	0.50	0.60	2.71
	Restituted	1.55	0.42	0.79	2.26	1.74	0.52	0.88	2.75
	Decayed	1.46	0.42	0.70	2.15	1.64	0.46	0.84	2.69
III	Initial	2.06	0.55	0.66	3.07	1.76	0.43	0.73	2.56
	Fatigued	1.69	0.34	1.22	2.43	1.96	0.38	1.35	2.71
	Restituted	1.82	0.31	1.20	2.41	2.14	0.50	1.25	3.41
	Decayed	1.80	0.31	1.17	2.46	1.96	0.45	0.98	2.79
II	Initial	2.48	0.35	1.94	3.12	1.87	0.25	1.46	2.28
	Fatigued	1.93	0.32	1.37	2.53	2.22	0.33	1.76	2.80
	Restituted	2.08	0.31	1.59	2.75	2.33	0.43	1.59	3.49
	Decayed	1.98	0.31	1.62	2.67	2.18	0.50	1.35	3.34
I	Initial	2.59	0.38	1.81	3.11	1.92	0.25	1.29	2.41
	Fatigued	1.91	0.31	1.33	2.55	2.15	0.32	1.57	2.81
	Restituted	2.04	0.31	1.43	2.70	2.53	0.43	1.79	3.30
	Decayed	1.94	0.34	1.44	2.66	2.36	0.47	1.62	3.24

[a] Diameter, extent, and speed, mm; log area, sq. mm; speed, distance in 0.01 mm/time in 0.1 sec.

[b] N = 24 (12 male, 12 female) in Group IV; 24 (11 male, 13 female) in Group III; 25 (13 male, 12 female) in Group II; 21 (11 male, 10 female) in Group I.

Table 2. MEANS OF CONSTRICTION OR DILATION IN 0.01 MM[a] FOR EACH 0.1 SEC WITHIN THE PUPILLARY RESPONSE FOR THE FOUR AGE GROUPS

Pupillary Response	Age Group	Constriction or Dilation in 0.01 mm for each 0.1 Sec														
		Light										Darkness				
		.1	.2	.3	.4	.5	.6	.7	.8	.9	1.0	.1	.2	.3	.4	.5 Sec
Initial	IV	1	1	7	36	43	28	20	11	10	5	−3[b]	−1	−1	3	9
	III	1	2	9	46	45	37	23	16	10	6	−2	0	1	2	10
	II	1	2	11	51	51	41	28	19	14	11	−5	−5	−2	−1	9
	I	2	3	12	51	54	42	32	19	15	11	−6	−6	−4	−4	8
Fatigued	IV	−1[c]	0	8	41	40	26	14	6	2	−4	4	3	3	6	10
	III	−1	−1	10	59	50	30	13	5	−1	−4	7	6	5	6	11
	II	−1	0	14	65	57	32	16	5	0	−5	6	6	4	7	13
	I	−1	0	16	65	52	31	16	6	0	−4	6	5	7	8	16
Restituted	IV	1	1	8	39	46	29	16	10	4	−4	6	6	5	7	10
	III	0	1	8	58	55	36	16	5	−3	−7	6	5	4	5	9
	II	0	1	12	63	59	36	20	7	2	−7	9	10	7	11	13
	I	2	3	14	64	61	35	17	4	−4	−12	10	10	6	9	12
Decayed	IV	−1	0	6	41	45	28	15	8	1	−3	4	4	5	7	9
	III	−2	−1	10	59	53	31	17	7	1	−3	5	7	5	7	11
	II	0	1	11	63	59	33	18	4	0	−4	5	5	4	8	13
	I	0	1	16	63	56	33	16	5	−3	−7	8	7	6	8	12

CONSTRICTION OR DILATION IN 0.01 MM FOR EACH 0.1 SEC WITHIN THE PUPILLARY RESPONSE FOR THE OLDEST (100.4 YEARS) AND YOUNGEST (7.5 YEARS) SUBJECTS

		Constriction or Dilation in 0.01 mm for each 0.1 Sec														
		Light										Darkness				
		.1	.2	.3	.4	.5	.6	.7	.8	.9	1.0	.1	.2	.3	.4	.5 Sec
Initial	O	1	2	2	24	11	26	14	20	11	9	−6	−5	2	4	3
	Y	8	10	10	78	44	42	37	9	13	9	−3	−2	−4	−9	5
Fatigued	O	4	5	4	4	13	5	5	3	0	0	0	2	2	2	0
	Y	5	7	14	68	56	28	18	−2	−4	−12	8	10	0	4	7
Restituted	O	0	0	5	7	21	12	5	−3	−2	−9	4	4	0	0	2
	Y	6	7	4	58	74	29	19	−6	−2	−18	19	12	5	10	9
Decayed	O	−1	0	6	1	11	6	3	−14	−2	−11	2	2	3	−3	−1
	Y	4	4	10	63	60	28	17	−8	−4	−10	10	12	5	13	8

[a] Decimals omitted.

[b] Minus values during Darkness indicate constriction.

[c] Minus values during Light indicate dilation.

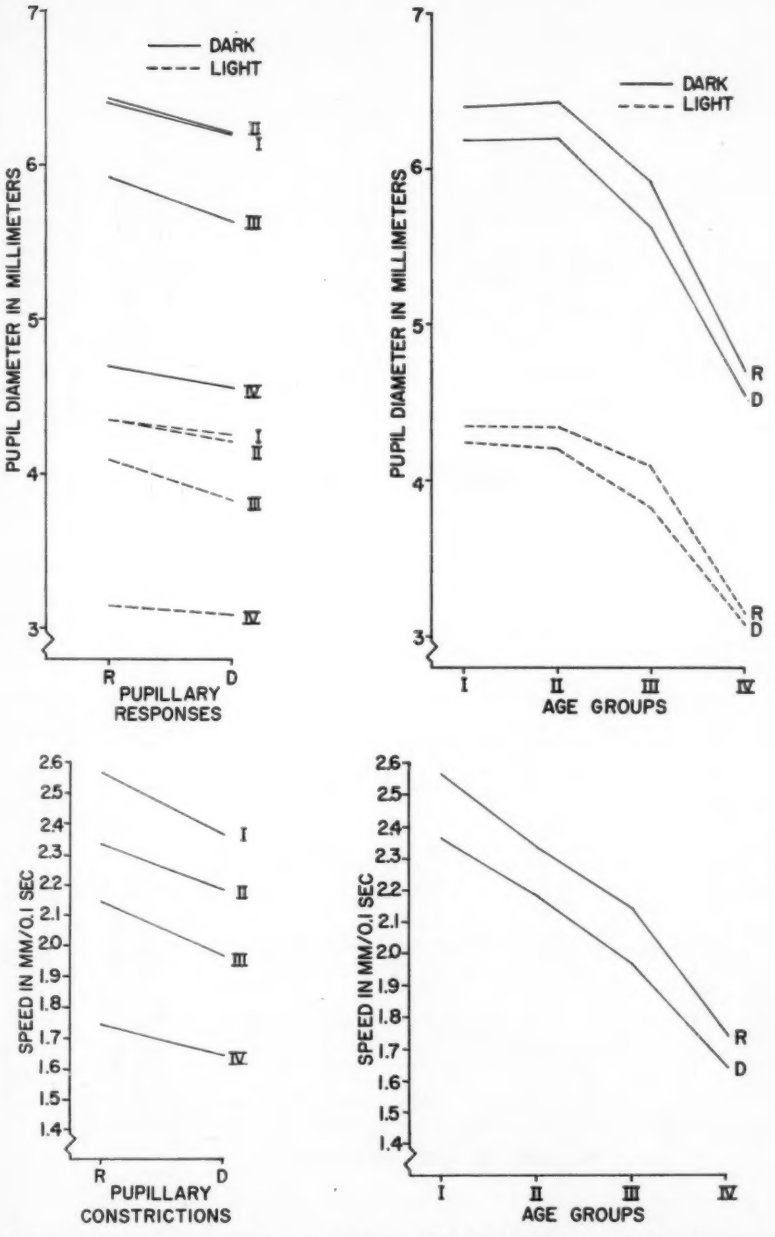

FIG. 1. Upper left: Mean pupil diameter at onset of light stimulation and at minimum size within the 4 age groups. Upper right: Mean pupil diameter at onset of light stimulation and at minimum size between the 4 age groups. Lower left: Mean speed of pupillary constriction within the 4 age groups. Lower right: Mean speed of constriction between the 4 age groups. R, pupil in restitution; D, pupil in decay of restitution; I, 7.5 to 15.0 years; II, 18.1 to 28.2 years; III, 30.5 to 52.7 years; IV, 70.4 to 90.8 years.

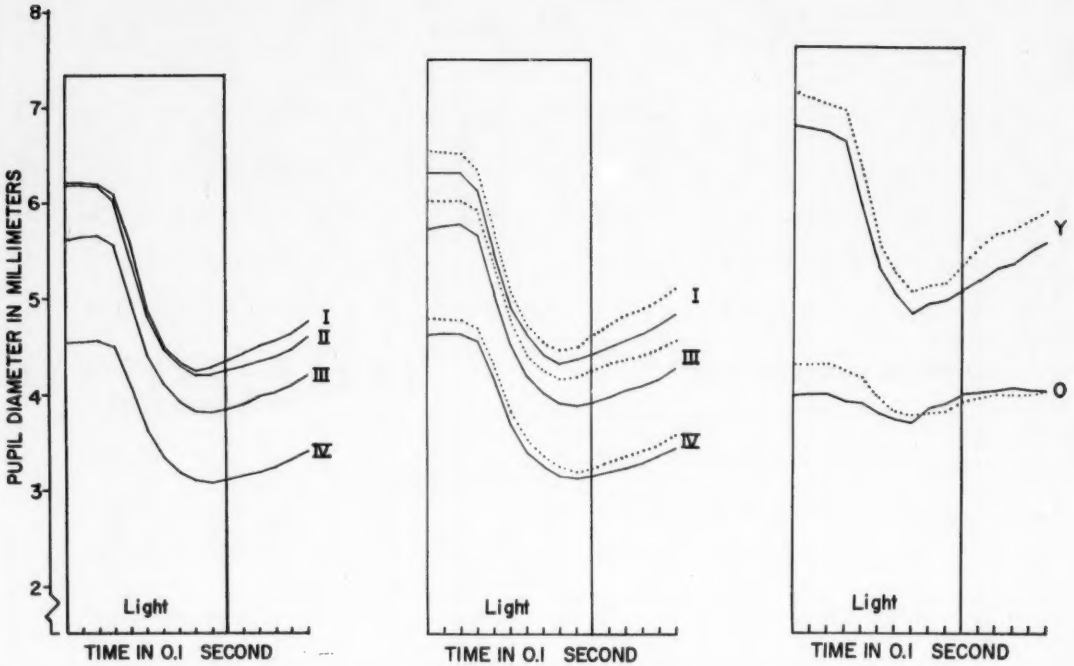

FIG. 2. Left and center: Pupillograms for age groups I, III, and IV. Right: Pupillograms for the oldest (100.4 years) and the youngest (7.5 years) subjects. Data for the oldest subject were not included in the computations for the experiment. Dotted lines, pupil in restitution; solid lines, pupil in decay of restitution.

TABLE 3. THE DIFFERENCES[a] BETWEEN THE MEANS OF THE PUPILLARY PHENOMENA.

Age Groups[b]	Pupillary Responses	df	Size at Onset of Light		Size at Minimum Size		Extent of Constriction		Speed of Constriction	
			Difference	Level of Significance	Difference	Level of Significance	Difference	Level of Significance	Difference	Level of Significance
I— II		44	0.00		0.04		−0.04		0.20	
I—III		43	0.51		0.29		0.22		0.39	*
I—IV	R	42	1.71	***	1.23	***	0.49	***	0.79	***
II—III		47	0.51		0.25		0.26		0.19	
II—IV		46	1.71	***	1.19	***	0.53	***	0.59	***
III—IV		45	1.20	***	0.94	***	0.27		0.40	*
I— II		43	−0.01		0.04		−0.04		0.18	
I—III		42	0.56	**	0.42	*	0.14		0.40	**
I—IV	D	40	1.64	***	1.16	***	0.48	***	0.72	***
II—III		47	0.57	**	0.38		0.18	*	0.22	
II—IV		45	1.65	***	1.12	***	0.52	***	0.54	***
III—IV		44	1.08	***	0.74	***	0.34	**	0.32	*
IV	R—D	21	0.15	*	0.06		0.09		0.10	
III	R—D	23	0.29	***	0.27	***	0.02		0.18	*
II	R—D	24	0.23	***	0.14	**	0.10	*	0.15	
I	R—D	19	0.21	**	0.10		0.11		0.20	

[a]Size and extent in mm; speed in 0.01 mm./0.01 sec.
[b]N = 23 in Group IV; 24 in Group III; 25 in Group II; 21 in Group I
*Significant at the .05 level.
**Significant at the .01 level.
***Significant at the .001 level.

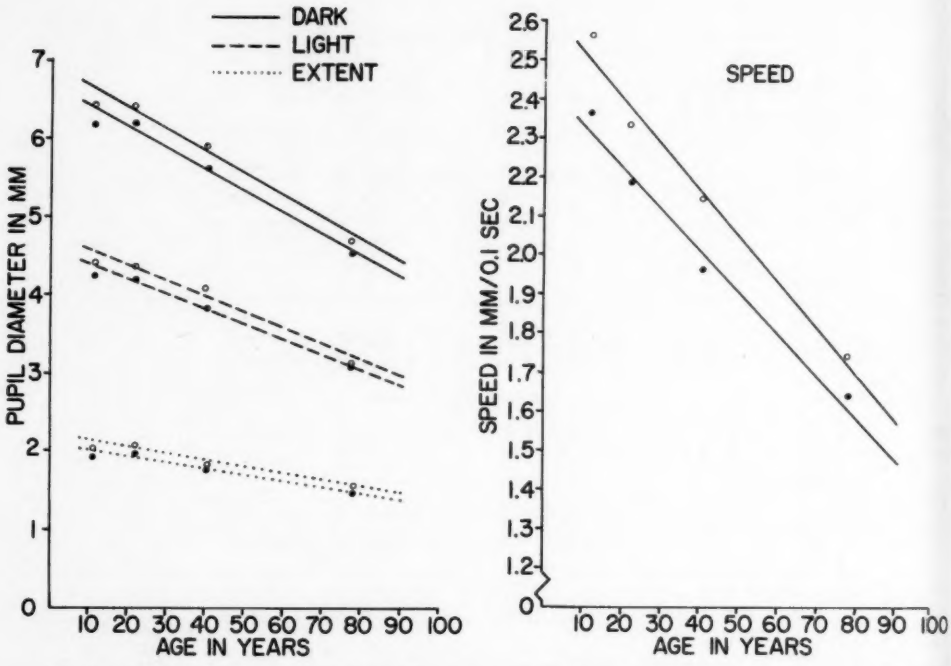

FIG. 3. Relation between age and pupillary response as shown in grouping the regression lines for pupil diameter at onset of light (Dark); pupil diameter at minimum size (Light); extent and speed of constriction. R, pupil in restitution; D, pupil in decay of restitution.

The straight line regression equation was fitted to these data and the values of its constants a and b are as follows:

Dark:	R, $\tilde{Y} = -.0282X + 6.94$;	D, $\tilde{Y} = -.0274X + 6.69$
Light:	R, $Y = -.0199X + 4.75$;	D, $\tilde{Y} = -.0192X + 4.57$
Extent:	R, $\tilde{Y} = -.0083X + 2.20$;	D, $\tilde{Y} = -.0078X + 2.09$
Speed:	R, $Y = -.0116X + 2.63$;	D, $Y = -.0105X + 2.43$

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CHANGES OF THYROID ACTIVITY IN THE RAT IN OLD AGE

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A DECREASE of the activity of the thyroid in old age has often been mentioned in humans. Anatomic involution was described (5, 7, 10) and this was related to the decrease of basal metabolism in old age (2). Also a decrease of plasma iodine (8) and an increase of serum cholesterol (3) was observed. The uptake of I^{131} in the thyroid in old age has been studied by Quimby, Werner, and Schmidt (11) and this was related to the function of the kidney (1, 6, 9) while Skanse (12) found no significant differences.

Since all these, partly contradictory, works were performed on humans we have now studied the problem of whether the thyroid activity changes with age in rats, in the "old age colony" of our laboratory, where all animals are of the same breed and are kept under identical conditions.

METHODS

Rats were injected intraperitoneally with 25 microcuries of I^{131} (without carrier), dissolved in 0.25 ml. of physiologic saline solution. Eighteen to 24 hours later the thyroid region of the rats was tested for radioactivity by means of a TCG2 Geiger counter (Tracerlab). The procedure was identical with that previously used in this laboratory (13, 14). The radiation values over the thyroid region were measured in series after 24, 61, 134, and 182 hours (1, 2½, 5½, and 7½ days) and in series II after 22-24, 69-71, 110-114 and 165 hours (1, 3, 4½, and 7 days).

Immediately prior to the radioactivity measurements the animals were anesthetized with ether, using a glass bulb. The excitation period is very short when a massive dose is given. The anesthesia was continued during the estimation, which lasted about three minutes. This procedure was then repeated every 24 hours, or in some instances after longer periods, until approximately the fourteenth day after the injection of I^{131}, at which time the radiation count approaches zero. It is of course possible that the thyroid at the end of this period may still contain small amounts of I^{121} the radiation of which is too small to penetrate the skin. The values measured were always corrected for physical decay and for the background count. The reliability of this method for rats was proven in previous publications (13, 14). The radiation values during a period of several days follow each other on a continuous line and single values are well reproduced in immediately following measurements. In former work, the uptake was studied from the first hours after injection, but this was not necessary with regard to the present problem.

In a number of animals the excretion of iodine in the urine was also measured. For this purpose the rats were placed in individual glass cages. The urine was collected and the water used to wash the cage added to the sample. All urine samples were made up to 50 ml. with water and an aliquot used for radiation measurement.

The estimation was made by evaporating 1 ml. of the urine sample to dryness at 95 C. in a small planchet. The radiation was measured and compared with equal quantities of the originally injected solution, which contained 25 microcuries in 0.25 ml. volume and expressed in percentage of the latter.

TABLE 1. COMPARISON OF I^{131} IN THE FIRST 24 HOUR URINE WITH TWO METHODS.

Animal No.	Dry Method	Dip Method
	% of Originally Injected I^{131}	Radiation Values (c.p.m.)
1	31.6	1520
2	17.3	905
3	35.3	1445
4	31.3	1150
5	25.6	1289

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Another procedure for measuring the urinary radioactivity was also employed. For this assay a dip Geiger counter (TCG5) was used on urine samples which had been diluted to 50 ml.; in this method only radiation values can be given. The range of measurements was the same for the two procedures; the dip counter method was found to have no advantage over the dry method (table 1).

RESULTS

All the rats employed in the experiments were of the same breed and were kept under identical conditions. Fifty per cent of the rats of our colony survive the age of 23.5 months; we have therefore designated as old animals rats more than 20 months old. The groups of old rats included in the present series of experiments were between 20 and 29 months of age. Parallel to the studies on the old animals, experiments were conducted with young animals aged 7 to 9 months.

The animals were studied in two series, the first during the summer period (May-June, 1954) and the second during the winter season (January, 1955): the results were similar in both series. Series I comprised 10 young (7 month old) and 12 old (24 month old) rats; series II 20 young (7-9 month old) and 20 old (20-29 month old) animals.

The results of the radiation measurements over the thyroid gland were plotted in curves for each animal. The curves show individual differences which at first sight seem to raise considerable difficulties for comparing the I^{131} uptake and release. The comparison was simplified, however, when the values obtained on the same days after injection of I^{131} were correlated and the mean values computed. On the basis of single curves it was our impression that old animals often release I^{131} from the thyroid more slowly than the young rats, i.e., the curve becomes flat after a few days. However, not all the old animals reacted in the same way, and some of the young animals also exhibited flat curves. Possibly such animals should have been considered abnormal and excluded from the comparisons.

The mean values of the radioactivity measurements over the thyroid gland observed on the 1st, 3d, 5th, and 7th day after injection of I^{131} are presented in table 2. The table

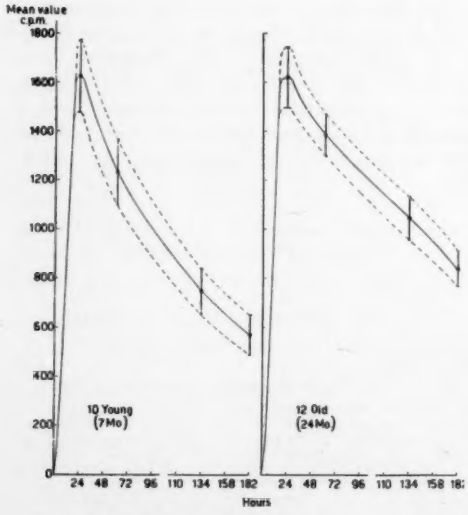

Fig. 1. Radiation measurements over the thyroid gland in rats following injections of 25 microcuries of I^{131} at zero time. Series I. Observations during summer period.

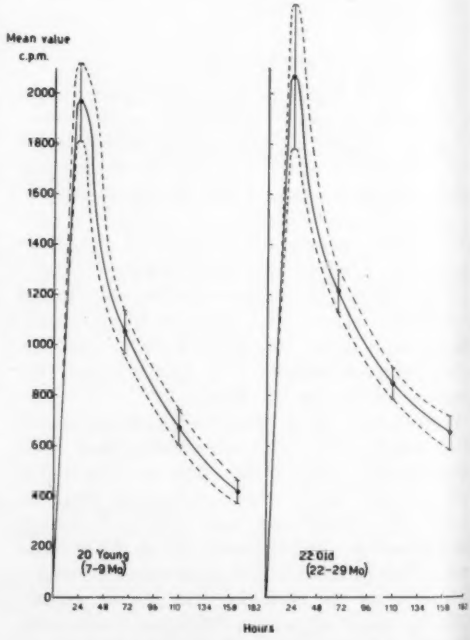

Fig. 2. Radiation measurements over the thyroid gland in rats following injections at 25 microcuries of I^{131} at zero time. Series II. Observations during winter period.

TABLE 2. RADIOACTIVITY MEASUREMENTS OVER THYROID GLAND OF RATS AT VARIOUS TIMES AFTER INJECTION OF RADIOACTIVE IODINE.

Series I. Young Rats: 7 Months; Old Rats: 24 Months

	Time After Injection of Radioactive Iodine							
	24 Hours		61 Hours		134 Hours		182 Hours	
	Young	Old	Young	Old	Young	Old	Young	Old
Number of rats	10	12	10	12	10	12	10	12
C. p. m. Mean value	1625	1623	1230	1385	746	1022	570	840
C. p. m. Standard error ±	147	120.5	133.5	83.9	87.5	88.3	80.7	72.5
No. of animals with c. p. m. above mean for old rats	0	6	0	6	0	7	0	8
No. of animals with c. p. m. above mean for young rats	4	6	3	8	2	10	1	10
p	0.9		0.3		0.05		0.05	

Series II. Young Rats: 7-9 Months; Old Rats: 20-29 Months

	22-24 Hours		69-71 Hours		110-114 Hours		165 Hours	
	Young	Old	Young	Old	Young	Old	Young	Old
Number of rats	20	22	20	20	20	20	20	20
C. p. m. Mean value	1966	2067	1052	1216	672	851	419	657
C. p. m. Standard error ±	155	283	85	83	66.5	62	43.3	66
No. of animals with c. p. m. above mean for old rats	0	5	0	9	0	9	0	8
No. of animals with c. p. m. above mean for young rats	7	7	9	14	9	17	10	17
p	0.7		0.1		0.05		0.01	

further contains the calculated standard error and p values. Not all intermediate measurements had been included.

As seen from table 2 the mean values for the old animals recorded on the 5th and 7th day were found to be higher than those observed in the young rats. The calculated p values are 0.05 and 0.01, respectively, for the groups in the two series of experiments. A listing has further been made in table 2 of the number of old animals which showed higher values than the mean value for the old group and the number of young rats exhibiting values above the mean for the young group at the same time of estimation. If the values for the 32 old animals in both series are

combined, it will be seen that 27, or 84 per cent, showed higher values on the 5th and 7th day than the average value for the young animals measured at the same time.

In figures 1 and 2 these mean values together with their standard errors are shown graphically for the two series of animals. It is evident from the figures that the release of I^{131} is slower in the old than in the young animals.

In order to evaluate these findings a consideration of the renal excretion of I^{131} seemed of importance. Such measurements, which were carried out in 15 old animals and 12 young animals in Series II showed the following: During the first 24 hours after the intraperitoneal injection of 25 microcuries of I^{131} very large quantities of iodine were excreted in the urine (table 3). Although some overlapping of the values for the groups occurred it was found that the young animals excreted much more iodine on the first day than did the old rats, namely an average of 48.4 per cent (±3.56) of the injected quantity compared with 29.2 per cent (±2.27) in the old animals. On the second day after injection the excretion became more or less constant and was only slightly less on the 5th and 6th days. The excretion on the second day was found to value about 5 per cent of the injected quantity of iodine and on the third day about 3 per cent. No characteristic difference in this steady excretion was noted between the old and the young animals. The sum of all I^{131} excretion during the first three days following the injection valued 57 per cent in the young and 38 per cent in the old animals (table 3). The total excretion over a period of 7 days was 68.1 per cent in the young and 50.9 per cent in the old rats.

TABLE 3. URINARY EXCRETION OF RADIOACTIVE IODINE IN PERCENTAGE OF INJECTED DOSE OF 25 MICROCURIES.
Figures represent individual animals.

	First Day		Second Day		Third Day	
	Young	Old	Young	Old	Young	Old
	30.4	27.7	3.9	4.6	3.0	4.4
	44.5	23.3	5.1	5.9	3.1	4.8
	42.6	35.7	4.1	4.1	3.0	2.5
	43.2	31.4	1.9	3.7	4.1	5.1
	51.0	7.8	5.63	6.2	2.53	2.68
	51.8	31.6	4.40	6.41	4.07	4.33
	69.5	17.3	3.78	8.23	3.51	3.24
	70.5	35.3	6.31	4.89	4.71	1.64
	39.0	31.3	7.44	5.78	5.23	2.37
	51.5	25.6	9.16	3.97	4.11	3.23
	52.8	27.7	5.70	6.82	2.92	2.83
	34.0	33.1	5.18	4.76	2.24	2.82
		27.8		5.90		2.19
		45.2		7.16		2.28
		37.0		4.79		
No. of Animals	12	15	12	15	12	14
Mean....	48.4	29.2	5.22	5.55	3.54	3.17
Standard Error...	±3.56	±2.27	±0.54	±0.34	±0.26	±0.29
p.....	0.01		0.6		0.4	

DISCUSSION

The radioactive iodine, soon after it is concentrated by the thyroid gland, becomes bound as organic iodine in the form of thyroxine and triiodotyrosin. These hormones are released from the thyroid during the following days, and the I^{131} activity of the gland thus becomes a measure of the rate of their release. The results of the present investigation have revealed that the majority of old rats (84 per cent) exhibit a delayed release of I^{131} from the thyroid gland as compared with young animals.

It was further found that old rats show a lower renal excretion of iodine during the first day after the iodine administration than do the young rats. This difference might be the result of an increased capacity of the thyroid of the old animals to retain iodine. The radioactivity measurements over the gland failed, however, to show an increased trapping of iodine by the thyroid in the old rats.

Another explanation of the lower iodine excretion by the old rats might be a reduced ability of the kidneys to excrete iodine. The quantities of iodine which are excreted in the urine are so small, however, that it is difficult to imagine that an impaired filtration by the kidneys could influence the excretion sig-

nificantly. It seems more likely that the decreased excretion by the kidneys is also an expression of the diminished release of iodine from the thyroid gland in the aged animals; after the rapid fixation of the injected I^{131} by the thyroid a slow release will lead to a slower excretion of iodine in the urine.

The delayed release of the thyroid hormone in the old animals, as measured by I^{131}, may be due primarily to a decreased metabolism of the body cells in the aged animals. Consequently, the thyroid would release less of its hormone, which increases the oxidation processes. Such explanation would agree with the well-known facts that in old age oxidation processes (2), body temperature and the upkeep of body temperature in cold surroundings (4), and the reaction of body temperature to diminished oxygen pressure (15) decrease. It may be of course that the decrease of cell metabolism is not the cause but rather the result of a decreased release of thyroid hormone. At present it seems hardly possible to decide definitely between these two possibilities.

SUMMARY

1. The activity of the thyroid gland was compared in 32 old (20-29 month) and 30 young (7-9 month) rats by measurement of the radioactivity of the gland following injection of I^{131}.

2. The release of I^{131} from the gland was in general found to be slower in the old than in the young animals. It was possible to demonstrate such difference in 84 per cent of the old rats on the fifth and seventh day after the injection.

3. The excretion of I^{131} in the urine on the first day after injection valued 48.4 per cent of the injected quantity in the young rats and only 29.2 per cent in the old rats. The most probable explanation of this difference seems to be that the decreased release of I^{131} from the thyroid in the old rats is the cause of the lower urinary iodine excretion.

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THE INFLUENCE OF PITUITARY FACTORS ON MENOPAUSAL VASOMOTOR INSTABILITY

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Menopausal vasomotor instability occurring with waning ovarian function is ordinarily adequately controlled with estrogens. It is generally assumed that the efficacy of this treatment is due to simple supplementation of declining estrogen titers. That the beneficial response to estrogen is not merely a replacement phenomenon is evidenced by the observations that vasomotor symptoms in women are also relieved by androgens.

A phenomenon common to the administration of either estrogen or androgen is the release of the luteinizing hormone (LH) from the pituitary gland. Following the administration of extradiol benzoate, in daily doses of from 1 to 15 micrograms to adult castrated rats for periods of 30 to 45 days the presence of LH is no longer demonstrable in the pituitaries and only the follicle stimulating hormone (FSH) remains in the pituitaries as shown by assay in hypophysectomized immature rats (4). A similar LH liberating effect occurs following the administration of testosterone propionate subcutaneously in daily doses of 50 to 500 micrograms for periods of 30 to 45 days (3). It has been established that women with diminished estrogen production, as in the menopause, excrete large amounts of FSH but only small quantities of LH in the urine. Funnell, Keaty, and Hellbaum (2) found that the injection of estrodial benzoate to women in natural or surgical menopause caused an increase in the concentration of LH in the urine.

It has been proposed that the severity of the vasomotor symptomatology in the menopause is correlated with an increased secretion of FSH. It would seem equally plausable that these symptoms might be related to a decreased titer of LH. The present study is concerned with the relationship of both FSH and LH to menopausal vasomotor disturbances.

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METHODS

A total of 24 surgically castrated women were the subjects of the present study. Patients were selected who showed little or no improvement in their vasomotor instability with mild sedation or placebos. All of these women exhibited vasomotor instability of such severity as to awaken the patient from sleep at night. They had 8 to 21 flushes daily, each lasting several minutes, and were accompanied by redness of the face and sweating. Typical flushes were observed in each patient. Other symptoms associated with the menopause, including mental depression, headache, nervousness, insomnia, arthralgias, stress incontinence, and mild "hot flashes" were also present but were not used as criteria in this study.

All of the materials were administered intramusculary. Each patient was requested to record the incidence, severity, and duration of her flushes both before and after injection of the material to be tested.

A partially purified sheep pituitary preparation, Gonadophysin[R]*, containing both FSH and LH was administered to 14 patients in daily doses of 200-500 Searle rat units. Six of the patients were injected daily for 6 to 8 days with a follicle stimulating extract prepared from acetone-dried sheep pituitary glands in a manner similar to that reported by Fevold (1). Four of the patients received daily, for 6 to 10 days, a pituitary preparation containing primarily LH.† Since there are no established or acceptable units for LH standardization, the dosage of both the FSH and LH preparations are stated in terms of the amount of original tissue extracted. With both preparations the daily dose represented the material derived from 10 to 20 Gm. of fresh pituitary tissue. Both preparations had been assayed in normal and hypophysecto-

*Furnished through the courtesy of Dr. I. C. Winter of G. D. Searle and Co.

†Furnished through the courtesy of Dr. Hartford McShan of the University of Wisconsin.

mized immature rats. The FSH preparation induced only follicular development in the test rats. The LH preparation produced no response by itself, but when injected with the FSH preparation an augmented gonadal weight response occurred together with luteinization of the ovaries of the immature test rats.

RESULTS

As may be seen in table 1, improved vasomotor stability occurred in those patients receiving preparations containing LH but was unchanged in those receiving the FSH extract. Twelve of the 14 bilaterally oophorectomized women who received Gonadophysin®, which contains substantial amounts of FSH as well as LH, in dosages of 200 to 500 Searle rat units per day, obtained complete relief from the vasomotor episodes. One patient was partially relieved while the remaining patient derived no benefit.

TABLE 1. THE EFFECT ON VASOMOTOR DISTURBANCES IN OOPHORECTOMIZED WOMEN AFTER ADMINISTRATION OF DIFFERENT PITUITARY GONADOTROPIC PREPARATIONS.

Total No. Patients	Pituitary Preparation Injected	RESPONSE		
		No. of Patients Improved		
		Complete Relief	Partial Relief	Negative
14	Unfractionated (both FSH & LH)	12	1	1
6	FSH	—	—	6
4	LH	3	1	0

The validity of the results with the unfractionated preparation was further tested by the administration of separate extracts containing primarily either FSH or LH respectively. In the 6 patients who received the extract containing predominately FSH, vasomotor disturbances were neither improved nor made worse. Thus, FSH preparation was without noticeable effect. In an earlier study an unsuccessful attempt was made to induce flushes in 3 normal patients with the administration of pituitary FSH preparations.

The 4 patients who received the LH preparation were all benefited in so far as improvement of vasomotor instability is concerned. Three of the patients were completely relieved within 36 hours following the first injection and remained free of symptoms throughout the course of treatment. Two of these patients had previously received the FSH extract without effect. Prior to treatment 1 of the 4 patients injected with LH had an average of 8 to 12 flushes during the day and 5 to 7 each night. These symptoms were not completely eliminated by the LH administration, although the vasomotor episodes were reduced to 1 to 4 during the day and 0 to 1 during the night. This patient is designated as receiving "partial relief" in table 1.

The beneficial effects were transitory and lasted only 3 to 5 days after the injections were stopped. In some cases as many as 3 different series of Gonadophysin® injections were given, allowing the patients to return to their previous state of vasomotor instability between each series.

DISCUSSION

The menopause or climacteric occurs at a time in life when physiologic processes are declining. Structures and organs of the body other than the endocrine glands are affected. The most dependable sign for assessing the menopausal syndrome is the flush. Other symptoms such as sudden perspiration, headaches, nervousness, irritability, anorexia, and melancholia, may occur under many other circumstances, as well as at other times of life when changes in metabolic activity and mental attitude occur. However, because of the frequency of these symptoms at the time of menopause, is is not unusual to obtain benefit from a variety of agents other than endocrine.

The climacteric, or menopause, does not represent an abrupt transition, but starts years before cessation of menstruation. It is generally accepted that the peak of reproductive or ovarian activity occurs between the ages of 25 and 30 years, with a gradual regression thereafter. In line with the saying that "senility begins with birth" one might be a bit more conservative and state that "menopause begins with the first menstruation," for it is true that the scarring, furrowing, crypt formation and fibrosis resulting from each repeated ovulation and the formation of corpora albi-

cans eventually lead to a cessation of ovarian activity. Thus, with each ovulation and menstruation there is a gradual decline until the menstrual process stops entirely. However, varying degrees of ovarian function persist after the menses cease.

The mechanism by which the symptoms of menopause are produced, particularly the periodic vasomotor instability, and the mechanism of alleviation of these symptoms has not been satisfactorily explained. Since the symptoms are associated with decline in ovarian function and decreased secretion of estrogen, one might assume that lack of estrogen is the disturbing factor; particularly as these symptoms may be ameliorated by estrogens. However, since androgens are likewise effective, one thinks of some action common to both types of these sex hormones, such as their effect on the anterior pituitary gland.

Three factors from the anterior pituitary gland affect the ovaries, namely: 1) follicle stimulating hormone which initiates the development of the Graffian follicle, 2) luteinizing factor which induces ovulation and subsequent corpus luteum formation, and 3) luteotropin. The function of the latter is not fully established except as regards the maintenance and persistance of the functioning corpus luteum during pregnancy and lactation.

Any possible inhibition of FSH secretion by estrogen seems to be incidental and of no particular importance in so far as menopausal vasomotor instability is concerned. One should rather consider the stimulation of LH release as the important event following estrogen or androgen administration to the menopausal subject.

It might further appear that LH from the pituitary is the common denominator upon which the action of estrogens and androgens depend, in so far as relief of menopausal vasomotor instability is concerned. Such a viewpoint is supported by the data presented.

Whether the relief of menopausal vasomotor instability is a direct effect of LH or only another link in a chain of events cannot be answered at this time. The possibility of stimulation of the adrenal cortex by LH has been reported (5). The contiguous hypothalamus with its intriguing connections with the pituitary gland as well as the vasomotor centers might add yet another chapter.

No therapeutic importance is attached to the present investigation; rather it is presented to effect a better understanding of the mechanism of the most interesting phenomenon of menopausal vasomotor instability.

SUMMARY

Twenty-four surgically castrated women with severe vasomotor instability received various pituitary preparations. All of the 4 patients injected with a fractionated pituitary preparation containing predominantely the luteinizing hormone (LH) were benefited; while a fractionated pituitary extract containing primarily the follicle stimulating hormone (FSH) was without noticeable effect in 6 patients. An unfractionated pituitary preparation containing both LH and FSH alleviated the vasomotor symptoms in 13 of 14 patients. Thus, the relief of menopausal vasomotor instability occurs following the administration of luteinizing hormone from the pituitary gland. It is suggested that the beneficial action of estrogens and androgens on this phenomenon might be due to their release of this pituitary factor.

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URINARY EXCRETION AFTER THE AGE OF NINETY.

A Study of Neutral 17-Ketosteroids, Creatinine, and Creatine

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A RECENT study of morbid anatomy in elderly subjects (8) revealed considerable differences between the incidence of various pathologic processes in successive age groups. The nonagenarians, in particular, showed special characteristics. Since little is known about the normal variations in physiology at this age, it seemed worth while to study certain problems, such as those of urinary excretion in this age group. The investigations undertaken were the measurement of the daily output of urine and the excretion of neutral 17-ketosteroids, creatinine, and creatine.

The subjects of these experiments were a group of 20 women and 7 men, at Queen's Hospital, Croydon, and St. John's Hospital, Battersea, London. All were 90 years old or over; none were incontinent. Most of them were bedridden, but none were suffering from any general disease process other than senile weakness at the time of the investigation. The age and sex are shown in table 1.

Daily Output of Urine.—When the 24 hour specimen of urine was collected and sent to the laboratory, the volume was nearly always found to be small. The actual measurements are shown in table 1 and varied between 250 ml. and 2,400 ml. The last figure was considerably higher than any of the others and came from an active old woman of 90 who was up and about in the hospital ward all day. Such low volumes of urine output were unexpected and therefore had to be checked. In 4 patients the 24 hour specimen was measured again after a few days. One of these showed an increase of 60 ml., another a decrease of 20 ml., the third an increase of 300 ml., and the fourth an increase of 750 ml. A year after the original measurements, 3 more of the subjects had their fluid intake and output checked over a period of 3 days.

The patient who had originally showed the highest output (2,400 ml.) was now partially bedridden. Her total intake during the 3 days was 3,060 ml. and her output 2,960 ml., much less than before, with an average daily output of 987 ml. on this occasion. The oldest patient, who was now 102 years old, showed an average daily output of 887 ml. This agreed very closely with her former figure of 880 ml. The third old lady now showed a mean output figure of 667 ml. as against per previous 550 ml. A fourth patient, not previously measured, excreted 2,280 ml. in the 3 days on an intake of 2,660 ml. mean intake being 887 ml. and output 760 ml.

To supplement these figures, a special study was made in a patient of 94. Intake and output of fluid was measured and charted for a period of 7 successive days. The total for this period came to 3,750 ml., intake and output balancing closely. Daily excretion of urine varied from 230 ml. to 715 ml., while fluid intake ranged from 330 ml. to 540 ml. Later repetition of the same measurements for another 7 days gave a total of 3,980 ml. with similar variations. Only on one occasion during the period of study did the subject drink as much as 300 ml. at one time. Usually an amount of 140-170 ml. 3 or 4 times a day was all that she took.

In the same way, the output of urine voided was small, sometimes merely 55 ml. at a time. It only amounted to as much as 225 ml. on one occasion. The frequency of micturition was thrice in 24 hours 3 out of 7 days of the first trial, 4 times once, 5 times twice, and 6 times once. It seems probable from this supplementary trial that the low figures of urinary output encountered in the original investigation were not unusual among subjects of 90 or more. Fluid balance at advanced ages must differ in several respects from that of earlier adult life.

Neutral 17-Ketosteroids.—These substances were estimated in the biochemistry laboratory of the Pathology Department at Lambeth Hospital. The method consisted of a combination of Hawk's modification of the McGill University clinic technique and the colorimetric method of the Medical Research Council (7).

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A 24-hour specimen of urine was collected and measured. To a 100 ml. aliquot, 15 ml. of concentrated HCl were added. The mixture was refluxed for exactly 8 minutes, and then immediately chilled and extracted 3 times with 50 ml. portions of freshly redistilled ether. The combined ether extracts were washed twice with 2N NaOH (15 ml. portions) and then twice with water (25 ml. portions). On evaporation of the ether, the neutral residue was dissolved in 2 ml. re-rectified absolute alcohol.

The colorimetric estimation was then carried out according to the method of the Medical Research Council. (11).*

In the series of very old people under review (20 women and 7 men) the total daily excretion of neutral 17-ketosteroids was measured as above. It was found that the range of figures for females varied from 1.2 mg. to 4.2 mg. in the 24 hours. The figures for males varied from 1.5 mg. to 5.7 mg. The individual results may be seen in table 1. In the whole the levels for women are lower than those for men. There was some evidence statistically to suggest that the output of ketosteroids might be positively correlated with the total output of urine, but the relation was not complete (fig. 1). The highest figure in women (4.2 mg.) was obtained in the subject with the largest amount of urine. The mean level for men was 3.2 mg. and for women 2.2 mg.

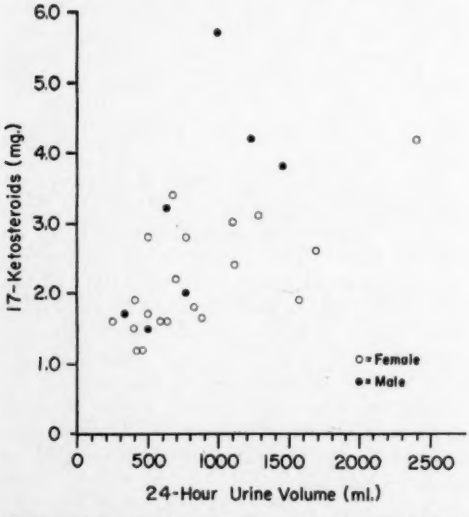

FIG. 1. Correlation between urine volume and 17-ketosteroid excretion.

TABLE 1. 24-HOUR URINE VOLUME AND EXCRETION OF NEUTRAL 17-KETOSTEROIDS, CREATININE, AND CREATINE.

Age	Urine Volume (Ml.)	Neutral 17-Keto-steroids (Mg.)	Creatinine (Gm.)	Creatine (Gm.)
		Men		
90	330	1.7	0.26	0.03
90	760	2.0	0.56	0.23
91	990	5.7	0.59	0.09
93	500	1.5	0.28	0.04
93	1240	4.2	0.56	0.23
96	630	3.2	0.44	0.03
97	1450	3.8	0.69	0.09
		Women		
90	1110	2.4	0.49	0.04
90	670	3.4	0.54	0.11
90	2400	4.2	0.76	0.18
90	760	2.8	0.42	0.18
90	430	1.2	0.22	0.12
91	400	1.5	0.15	0.06
91	450	1.2	0.30	0.12
92	1280	3.1	0.71	0.18
92	1670	2.6	1.00	0.23
94	580	1.6	0.42	0.02
94	640	1.6	0.35	0.05
94	250	1.6	0.21	0.04
95	700	2.2	0.21	0.22
95	410	1.9	0.25	0.03
95	500	2.8	0.38	0.07
96	500	1.7	0.035	0.095
96	830	1.8	0.39	0.04
97	1560	1.9	0.84	0.14
99	1100	3.0	0.57	0.20
101	880	1.65	0.36	0.13

While several series of ketosteroid measurements among elderly subjects have been published, few seem to have included many nonagenarians. Even Hamburger (5) shows only 3 men and 3 women in this age group. His tables show figures between 3 mg. and 5 mg. for the males and between 1 mg. and 3 mg.

*This technique was evolved by Dr. L. Ellis of Lambeth Hospital, to whom my thanks are due for permission to publish the details. I also would thank Dr. Hewlett, Chief Pathologist of the laboratory for all his help and assistance during the research; and Mr. Michael Curwen, Statistician to St. Bartholomew's Hospital, for the statistical treatment of the results.

for the females over 90. Cioffari and Cossandi (2) state that the level of ketosteroids drops to a figure of 7.5 mg. by the age of 80. They suggest that, after the age of 65, both sexes show similar excretion on a declining scale, providing that their weights are equal. On the other hand, Robinson (14) considers that males show a wide variation of ketosteroid excretion up to the ninth decade. Prunty (13) also states that day by day variations of approximately 33 per cent may be found. He quotes figures ranging from 8 to 23 mg. for men and 5 to 18 mg. for women in adult life dropping by 50 per cent at the age of 70. Kowaleski (9) mentions figures of 5.58 mg. for men and 5.6 mg. for women between 60 and 89, with ranges of 4-11 mg. in the men and 4-8.7 mg. in the women. None of his subjects, however, had less than 4 mg. in the 24 hour specimens, while only 3 of the present series exceeded this figure. His technique was not the same as that employed in the laboratory of Lambeth Hospital, which may account for the difference.

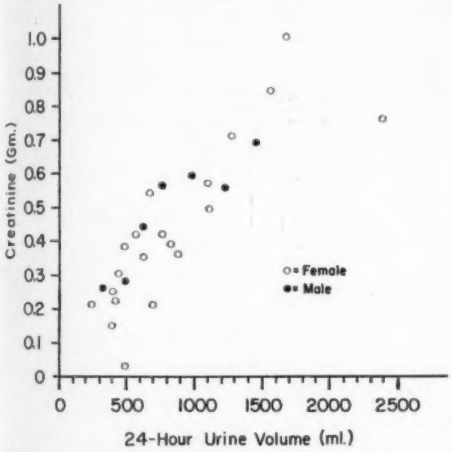

FIG. 2. Correlation between urine volume and creatinine excretion.

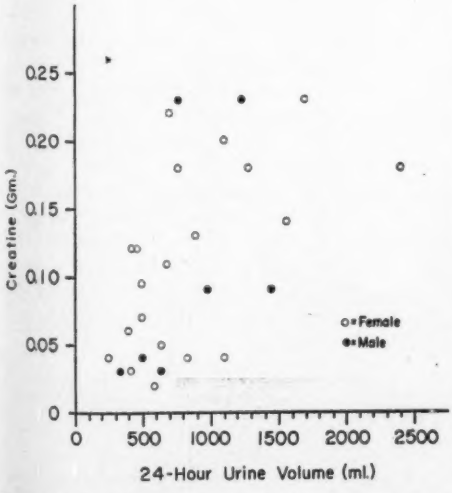

FIG. 3. Correlation between urine volume and creatine excretion.

Creatinine.—The amount of this substance in the urine was estimated by the boiling method of Folin (4). The individual results may be seen in table 1. When the daily excretion was measured in this series of patients, it seemed that the level was correlated with the fluid output (fig. 2). The relationship was, roughly speaking, 0.55 Gm. per 1000 ml. The women showed a much wider range of readings than did the men, varying from 0.035 to 1.0 Gm. in the 24 hours, while the men only showed figures between 0.26 and 0.69 Gm. When the two sexes were taken together, the median of distribution was 0.42 Gm. The mean for the men was 0.48 Gm. and for the women 0.46 Gm.

It is usually considered that the amount of creatinine in the urine is constant for the individual. Figures varying from 1.5-2.0 Gm. daily for men and 0.8-1.5 Gm. for women are considered as normal by Cantarow and Trumper (1); Kolmer and Boerner (10) give a figure of 1.25 Gm.; Fearon (3) suggests 1.2 Gm. and Harrison (6) 1.0-1.5 Gm. as levels to be expected. Peters and Van Slyke (12) mention that the urinary clearance of creatinine may fall with extreme oliguria. Even so, the figure of the present series show considerable diminution as compared with the standards of normal adults.

Creatine.—The levels of this substance in the daily output of urine were measured by the Folin method (4). The individual results are presented in table 1. None of the patients in the series failed to show some trace of the substance. The amounts ranged from 0.025 to 0.23 Gm. There was no definite evidence of any difference between the sexes. The me-

dian value of the distribution of men and women together was 0.09 Gm. There seemed to be a separate group of subjects having a higher creatine output than the rest. All of these showed high figures for total urine excretion. There was a slight suggestion that some correlation existed between magnitude of creatine excretion and output of urine, but this was far from exact (fig. 3).

Some authorities have stated that creatine is not excreted in the urine of normal males. Smith (17) found it absent in the urine of adult females except during menstruation, pregnancy, and the puerperium. It is known to occur in the urine of infants and small children. It may be found associated with starvation, carbohydrates privation, in wasting diseases, diabetes mellitus, and hyperthyroidism. Considerable amounts may be present in certain muscular dystrophies and atrophies. Taylor and Chew (18) quote 15 adult males showing amounts varying from 0 to 196 mg. in a day. The ages of their subjects were between 20 and 34 years. Schittenhelm and Bühler (15,16) found that creatine may occur in the urine of aged men and women after the menopause, being diminished or abolished by administration of sex hormones. When caused by disease, a raised creatine content of the urine is said to be associated with a low creatinine figure. In the present series, the lowest reading for both substances and the highest levels were associated in the same two individuals.

DISCUSSION

It is usually reckoned that the excretion of neutral 17-ketosteroids in women is a measure of adrenal cortical activity. In the cases under review the small amounts appearing in the urine suggest that such function must be at a lower level than during earlier life. The urinary ketosteroids in men are thought to come partly from adrenal cortex and partly from the testis. All the men in the present series had far less than the 15 mg. considered to be the usual male output per day, some only being able to produce 1.5 mg. Such results suggest a profound depression of endocrine activity as compared with the younger adult. It seems probable that both testis and adrenal cortex are manifesting hypofunction.

When we consider the measurement of urine excreted, we again find daily amounts which are extremely low. The actual mechanism of this *oliguria senilis* is uncertain. Nevertheless it is tempting to wonder if this, too, may be of endocrine origin.

The low figures for creatinine excretion, only half the normal level, are not easy to interpret. Cantarow and Trumper (1) mention that the administration of testosterone diminishes the amount of creatinine in the urine of eunuchoids and castrates. Tissue catabolism is said to be associated with increased excretion. On the other hand, Peters and Van Slyke (12) mention that the urinary clearance of creatinine falls with extreme oliguria. This is in keeping with the statistical correlation between level of creatinine and fluid found in the present series.

The presence of creatine in all the specimens of urine from these very old people, both male and female, confirms the work of Schittenhelm and Bühler (15,16). It all tends to show that the present findings for urine volume, neutral 17-ketosteroids, creatinine, and creatine, excreted in the urine are very different from the values to be expected in younger subjects. Old age seems to have a physiology of its own.

SUMMARY

In a group of 27 subjects all aged 90 or over, the total urine output and the urinary excretion of neutral 17-ketosteroids, creatinine, and creatine, in 24 hours were measured.

The total fluid output was lower than normal, varying from 250 ml. to 1,670 ml., apart from one case of 2,400 ml.

Excretion of neutral 17-ketosteroids was diminished both in men and women. The excretion in men varied from 1.5-5.7 mg. and in the women from 1.2-4.2 mg.

The amount of creatinine in the urine showed a ratio of 0.55 mg. per liter. The mean for men was 0.48 Gm. and for women 0.46 Gm. This is less than the customary amount.

Every subject showed small amounts of creatine in the urine, varying from 0.025 to 0.23 Gm. in the 24 hours.

These findings suggest that the physiology of subjects over the age of 90 differs considerably from that of younger adults.

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FOOD PRACTICES OF OLDER PEOPLE LIVING AT HOME

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IN RECENT years attention has been focused on the nutritional needs of the older segment of the population. Today 1 out of every 12 people in the United States is 65 years of age or over (4). In 1900 the figure was 1 out of 25. Since 1900 the population of the United States has doubled, but the number of older people has quadrupled (16). We are rapidly becoming a nation of older people and it seems advisable to investigate the nutritional practices of the older adult. Although a sizable number of studies of the eating practices of old people living in institutions have been made, comparatively little effort has been devoted to the investigation of the dietary practices of elderly people living independently (i.e., not institutionalized). Yet, only 6 per cent of the older population in this country live in institutions.

Pyke and associates (10) studied 28 old women in London, 10 of whom lived independently in their own homes and 18 of whom lived in almshouses where they did their own shopping and cooking. For one week the women kept a record of the foods purchased and eaten. The daily intake ranged from 1034 to 2313 calories. Protein intake was 42 Gm./day or less. Calcium, iron, and the B-vitamins seemed to meet the British Standards of adequacy (12), but intakes of vitamins A and C were low.

A similar study was undertaken by Bransby and Osborne (1) in Sheffield, England. One hundred twenty-five men over 65 and 178 women over 60 living alone or with a spouse and willing to cooperate in a one week food survey were studied. Using a spring balance scale and standard measuring equipment, the subjects kept a record of all foods purchased and eaten for one week. An average daily caloric intake of 2096 for men and 1746 for women was reported. The protein intake averaged 71 Gm. for men and 57 Gm. for women. With the exception of vitamin A and riboflavin and, for women, iron, the group studied seemed to meet the British dietary allowances.

In a clinical, social, and nutritional survey of 70 patients over 65 years of age in a hospital out-patient department in Australia, Saint and associates (13) used the Oxford Nutrition Survey Standards (15) to evaluate diets. Diets were analyzed and rated into 4 groups: excellent, good, borderline, and inadequate. Seventeen per cent of the diets were adequate in all respects and 39 per cent borderline or inadequate.

Jordan and associates (7) studied the food habits of a selected group of 100 people in Westchester County, New York. Using Joliffe's Check List (6) for a satisfactory diet as a standard, she found the outstanding dietary lack to be a poor intake of green and yellow vegetables. Dairy products and citrus foods were used less than might be considered desirable. Changes in eating habits among the people studied were attributed to medical and social factors more often than to other factors, including economic.

Ohlson and associates (9) studied the dietary practices of 100 women over 40 living in the North Central region of the United States. Three groups of women were observed: 1) 10 women between the ages of 52 and 74 who were willing to cooperate in a metabolism study. These women were selected because of excellent adult vitality; 2) a random sample of 76 women over 40 years of age from whom data were obtained by questionnaire; 3) a selected sample of 14 Negro women between the ages of 43 and 78 who took part in a balance experiment. Groups 2 and 3 were subdivided into "good" and "poor" health groups. The daily intake of all groups averaged 300 to 500 calories less than that reported for representative samples of younger women. The mean caloric intake ranged from 1122 to 1824 with the women in "good" health consuming the greater number of calories. No tendency for the caloric intake to decrease with age was observed. The average protein intake ranged

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TABLE 1. RESULTS OF TWO METHODS OF CONTACTING PEOPLE OVER SIXTY-FIVE YEARS OF AGE.

	Contacted	Seen		Refused		Deceased		Not Found or Ill		No Answer	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Method 1 (mail)	636	58	9	14	2	8	1	16	3	540	85
Method 2 (house-to-house)	130	42	32	38	29	2	2	48	37		
Total	766	100	13	52	7	10	1	64	8		

from 41 to 61 Gm./day and again the women judged to be in "good" health had the higher intake.

In a study of 280 men and 297 women over 50 years of age, Gillum and Morgan (5) reported the following means and standard errors: men, 2376±102 calories; women, 1683±62 calories; men, 83±4 Gm. protein; women, 59±3 Gm. protein.

MATERIAL AND METHODS

Using the police lists which are compiled each January, a random sample of the population 65 years of age or over living independently in a low to moderate economic area in Boston was drawn. Every fortieth person 65 years of age or over was listed until 100 names were drawn. Thereafter every twentieth name was included in the sample so that basically it may be described as a 1 in 20 random sampling of the population 65 years of age and over.

Two methods of contact were used: 1) a double post card describing the study and inviting cooperation was sent to each individual. A dietary history was taken on those individuals returning post cards which indicated a willingness to participate. 2) interviewers went unannounced to the home and took a dietary history.

Each person included in the sample was visited in his home by a nutritionist who weighed and measured him with indoor clothing and shoes on. A questionnaire pertaining to social history and past illnesses was completed. The dietary history taken was modified after Burke (2) and included an account of the usual food pattern in addition to a crosscheck of specific foods eaten. Dietary findings were translated into 11 nutrients using Leichsenring and Wilson's (8) short method of dietary analysis, and evaluated with the National Research Council Recommended Allowances (11) as a standard. Joliffe's Check List for a Satisfactory Diet was used to rate daily food selection.

RESULTS

A total of 100 individuals 65 years of age or over were interviewed. Of these 58 were contacted by method 1 and 42 by method 2. It was necessary to contact 786 people to obtain this sample of 100, that is, 13 per cent of those contacted were interviewed. Table 1 summarizes the results from the two methods.

The percentage of people contacted and seen by method 2 was significantly greater than the percentage by method 1 ($x_1^2 = 50.96$, $p<.01$). Possible reasons for this are: Method 2 required an immediate decision, i.e., there

TABLE 2. CRITICAL RATIOS* OF MEAN DIETARY INTAKES FOR GROUPS CONTACTED BY MAIL AND BY UNANNOUNCED HOUSE CALLS.

	Women	Men
Calories	1.23	0.39
Protein	2.18	0.06
Vitamin C	0.59	0.16
Age	0.00	0.00

*Critical Ratio = $\frac{\text{Difference between two sample means}}{\text{Standard error of the mean}}$

TABLE 3. AVERAGE INTAKE OF SPECIFIC NUTRIENTS.

	Men	NRC Recommended Allowances (65 Yrs.)	Women	NRC Recommended Allowances (65 Yrs.)	Total
Calories	2458 ± 943	2600	1831 ± 463	1800	2025 ± 708
Protein (Gm.)	87.6 ± 32.0	65	65.8 ± 16.1	55	72.6 ± 24.3
Fat (Gm.)	106 ± 47		81 ± 26		89 ± 36
Carbohydrate (Gm.)	279 ± 128		211 ± 59		232 ± 91
Calcium (Gm.)	1.06 ± 0.62	0.8	0.87 ± 0.39	0.8	0.93 ± 0.47
Iron (mg.)	13.51 ± 4.92	12	10.00 ± 2.40	12	11.1 ± 3.7
Vitamin A. (I. U.)	10973 ± 8741	5000	8571 ± 5188	5000	9316 ± 6549
Thiamine (mg.)	1.29 ± 0.46	1.3	0.94 ± 0.24	1.0	1.05 ± 0.36
Riboflavin (mg.)	2.00 ± 1.02	1.6	1.58 ± 0.57	1.4	1.71 ± 0.76
Niacin (mg.)	15.69 ± 5.80	13	11.60 ± 3.12	10	12.9 ± 4.2
Ascorbic Acid (mg.)	105 ± 23	75	95 ± 75	70	98 ± 74

was no time to deliberate about cooperating; method 2 did not require the individual to take the initiative in signifying interest by returning a post card; the personal contact in method 2 permitted better explanation of the survey.

It is reasonable to ask whether the population contacted by method 1 differs significantly from that contacted by method 2. Do individuals who make the effort to return a post card have better food habits than those who do not? Intakes of protein, calories, and ascorbic acid of individuals contacted by methods 1 and 2 were compared to see if the populations were similar.

Calories and protein were chosen as indicative of the over-all quality and quantity of the diet. Vitamin C intake was compared since some investigators (3) have reported an association between vitamin C intake and income level. Age was included in the factors to be compared. Table 2 is a summary of the comparison of two populations. There were no differences in the two methods of contacting subjects that could be justified at the 1 per cent level of significance.

The dietary findings are summarized in tables 3 and 4. Average consumption figures are given in table 3. Men in the study met or exceeded the National Research Council

TABLE 4. PROPORTION OF INDIVIDUALS MEETING SPECIFIED AMOUNTS OF N. R. C. RECOMMENDED ALLOWANCES.

	Less than 50%		50–74%		75–99%		100% and More	
	Men	Women	Men	Women	Men	Women	Men	Women
Calories	0	0	39	14	26	33	35	52
Protein	0	0	3	6	26	20	71	74
Calcium	3	4	23	23	23	20	52	52
Iron	0	3	13	33	35	41	52	23
Vitamin A	7	3	3	1	16	14	74	81
Thiamine	0	3	32	17	19	36	48	43
Riboflavin	3	1	23	16	26	20	48	62
Niacin	0	1	10	4	23	28	68	67
Ascorbic Acid	10	6	7	20	23	7	61	67

TABLE 5. PROPORTION OF OLD PEOPLE MEETING JOLIFFE'S STANDARD CHECK LIST FOR A SATISFACTORY DIET.

Diet Constituents	% Meeting Standard		
	Men	Women	Total
4 eggs weekly	65	52	56
1 serving daily of citrus fruit, tomato, or their juices or fresh uncooked salad greens	68	68	68
1 pint milk daily or its equivalent in cheese (1 ounce for 1 cup) for adults	48	41	43
1 serving daily of lean meat, fish, poultry or seafood	71	75	74
1 serving daily of cooked yellow or leafy green vegetable	35	41	39
1 serving daily of another vegetable or fruit	94	91	92
1 portion daily of enriched or whole grain bread or cereal	100	99	99

Recommended Allowances in every respect but calories. Average consumption figures for women in the study met or exceeded NRC allowances for calories and all nutrients but iron and thiamine. Both men and women showed wide individual variations in intake.

Table 4 indicates the percentage of individuals meeting specified amounts of the recommended allowances. Iron, calcium, and vitamin C were the nutrients most frequently low in the women's diets. Men made the poorest showing in respect to calories, thiamine, calcium, and riboflavin. Most men and women met or exceeded the recommended allowances for protein, vitamin A, niacin, and ascorbic acid.

Joliffe's Check List for a satisfactory diet was used to evaluate daily food selection. Table 5 shows the percentage of individuals meeting this standard. Almost two-thirds of the people interviewed failed to consume a serving of yellow or a leafy green vegetable daily. Less than half were getting one pint of milk or its equivalent in cheese a day. It is of interest to note that slightly more women than men met the standard set for meat and meat alternates. It should be noted, however, that the standard is based on number of servings rather than size of serving. It is conceivable that the men had a more generous serving than the women. Almost half of the women ate less than 4 eggs each week. Only 1 person out of the 100 interviewed failed to meet the standard for bread and cereal. This was a 65 year old woman who ate all her meals out. She worked as a cashier in a restaurant and her typical meal pattern was: 6 a.m., orange juice, one doughnut, coffee; 10 a.m., egg, potato, coffee; 2 p.m., soup, meat, potato, vegetable, salad, dessert, milk. It was believed that one doughnut, even though made with enriched flour, did not meet the standard for bread or cereal.

Sixty-five per cent of the men and 87 per cent of the women ate three meals daily. The remainder ate two meals each day. In addition 52 per cent of the men and 58 per cent of the women had one or more snacks each day. Twelve men and 33 women received help in food shopping. Eighteen men and 34 women shopped for food without help. One man and 2 women ate all their meals

TABLE 6. HEIGHT AND WEIGHT FINDINGS (MEAN ± STANDARD DEVIATIONS).

	Height (Inches)	Present Weight % of Desirable	Maximum Weight % of Desirable	10% or More Above Desirable Weight When Interviewed	
				No.	*Percent*
Men	66.5 ± 5.3	109 ± 15.8	122 ± 6.8	15	48
Women	62.1 ± 1.7	114 ± 23.5	133 ± 24.1	39	57

out. Eleven men and 19 women ate some of their meals away from home. Three women reported that they had never been in a restaurant. Nine men and 20 women had friends in for a snack or a meal occasionally. Some said they would like to entertain but could not afford to.

Sixteen men (52 per cent) and 31 women (45 per cent) reported that they had never liked milk. Ten men (32 per cent) and 27 women (39 per cent) reported one or more fractures during their lifetime. Half of the men and 48 per cent of the women in this group said that they had never liked milk. Two women in this group and 1 man who reported no fractures were unable to answer the question about milk. Mean ages at the time of fracture were: men, 57±11, and women, 54±24. No correlation was found between calcium intake and fractures.

Seven men and 7 women were still gainfully employed at the time of the interview. The men's average age at retirement was 67±5 years. Mean age at retirement was not calculated for the women since the majority had stopped working outside the home when they were married.

Forty-three women were widowed, 8 married, 1 divorced, and 17 were single. Of the men, 8 were widowed, 21 married, 1 divorced, 1 separated, and none were single.

Table 6 indicates the height and weight findings. Fifty-seven per cent of the women interviewed were 10 per cent or more above their desirable weight using the Metropolitan Life Insurance Company tables as a standard. The corresponding figure for the men is 48 per cent.

Nineteen men (61 per cent) and 43 women (62 per cent) had undergone surgery one or more times. The mean age at the time of surgery was 56±17 for men, and 49±17 for women. Fourteen men and 17 women had undergone surgical procedures after the age of 59.

Nineteen men (61 per cent) and 37 women (54 per cent) reported having suffered one or more serious illnesses. Mean age at the time of illness was: men, 56±18, and women, 59±22. Thirteen men and 25 women reported a serious illness after the age of 59. Serious illnesses included any sickness which confined the individual to bed for one week and the diagnosis of any of the degenerative diseases, such as hypertension.

Thirty-seven women had a total of 90 live babies, 26 miscarriages, and 4 still births. Twenty-four women breast fed 79 babies for periods varying from two weeks to 4½ years. One mother of twelve breast fed all 12 children for 16 months each. This same woman, age 74, had had 3 miscarriages and 1 still birth. She had fractured her right ankle twice at the age of 59, at which time diabetes and "heart trouble" were diagnosed. She had had 6 abdominal operations and had been overweight all of her life.

DISCUSSION

Although mean protein figures for both men and women are well above the National Research Council Recommended Allowances, approximately one-fourth of the people interviewed were not meeting the standard. With the exception of the iron intake of the women, mean figures for all nutrients met the standard. However, when the percentage of individuals meeting the NRC allowances is calculated, three-fourths of the women failed to meet the standard for iron and approximately half of the people interviewed failed to meet the standard for calcium and thiamine. Nearly one-fourth of these elderly people were obtaining less than 75 per cent of the NRC recommended allowance for calories, calcium, iron, thiamine, riboflavin, and ascorbic acid. Food groups most often slighted were milk, or its equivalent in cheese, and cooked yellow or leafy green vegetables. Evaluating food intake with the Joliffe Check List for a satisfactory diet, one-third of the people interviewed were not consuming a satisfactory diet.

Despite the fact that mean figures for caloric consumption do not exceed the NRC standard, 48 per cent of the men and 59 per cent of the women were 10 per cent or more above their desirable weight. Once again the value of calculating the percentage of individuals meeting the standard is demonstrated since these figures reveal 35 per cent of the men and 52 per cent of the women consumed more calories than recommended. The large number of overweight elderly people is of interest

in view of the widely accepted thesis that overweight shortens life. Sheldon (14) in a survey of 463 old people in Wolverhampton, England, found obesity in a substantial proportion of women even in the more advanced age groups although it was not as frequent as in younger women. This finding did not hold for men.

No correlation was found between caloric intake and degree of overweight. This is not surprising in that the amount of activity varied widely; some subjects never went out-of-doors whereas some others were active in work requiring heavy exertion or were busy with hobbies such as fishing and club work.

Past medical histories reveal that the majority of the elderly people seen were remarkably healthy, being well past middle age before experiencing serious illness, surgery, or bone fracture. This may be a commentary of the health of these individuals or possibly the progress of medicine in that the prognosis for illness in the middle and older age groups has improved considerably. One woman had a radical mastectomy performed at the age of 83, one year before being interviewed. The dietary survey of the older population should prove useful in the planning of community nutrition programs.

The method of obtaining the dietary intake may be questioned as to reliability and validity. The interviewing method, while revealing long range food practices, may be criticized since it does require subjects who will cooperate and a trained interviewer. The method was chosen so that all subjects could be included. The choice was either a 24-hour recall or the interview method, as it is obvious that 100 elderly persons would not complete 7 day records. Only 1 of the persons contacted was unsuitable for interview. The method of obtaining past medical history by questioning the individual at only one interview may mean omission of some illnesses. However, fractures and such traumatic experiences it was thought would be remembered.

SUMMARY

A survey of 100 men and women 65 years of age and over living in a low to moderate economic area in Boston is reported.

Analysis of detailed dietary histories showed approximately one-fourth of the people interviewed were consuming less than 75 per cent of the National Research Council Recommended Allowances for calories, riboflavin, iron, and ascorbic acid. Milk, or its equivalent in cheese, and yellow and leafy green vegetables were the foods most often slighted by both men and women.

Forty-eight per cent of the men and 57 per cent of the women in this group were 10 per cent or more above their desirable weight. No correlation was demonstrated between caloric intake and degree of overweight.

Medical histories included information on number of fractures, long illnesses, and surgical procedures and the age at onset. Information on marital status, living conditions, and employment is also reported.

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SOME EXPERIMENTAL TESTS OF THE EFFECT OF AGE ON CREATIVE INTELLECTUAL OUTPUT*

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THE QUANTITY, quality, and dates of achievements by people who work or have worked in science, philosophy, medicine, and other intellectual fields can be estimated from standard references which list and evaluate inventions, discoveries, books, and other achievements. Lehman (6) analyzed and recombined this kind of information and was able to establish, for a variety of disciplines, the average rates of production at different age levels for achievements of varying merit.

Among Lehman's firmly based conclusions are that 1) in most creative intellectual fields of endeavor, man's most creative years occur relatively early in life—about age 30 to 35; 2) quality of achievement reaches its peak earlier and declines more rapidly than mere quantity of achievement; and 3) very high quality achievement reaches its peak earlier and declines more rapidly than achievement of lesser merit.

In a rather less striking way, Lehman (p. 142-144, 192) demonstrates that although within any given field of endeavor quality and quantity of achievement are not necessarily correlated, yet the more distinguished thinkers are on the whole more prolific than less distinguished thinkers, and they begin their productive work earlier in life.

Lehman's evidence supporting his conclusions holds only in relation to early achievement and total output, and it does not necessarily follow that, at any given age or for any given period, the thinker of great merit will produce more than the thinker of lesser merit. The cynic indeed may argue that where the intellect is concerned quantity is only achieved at the expense of quality.

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*The author is entirely responsible for this report, but is grateful for the advice and comments given by his colleagues at the University of Liverpool and by the Rev. A. T. Welford of Cambridge.

Lehman (p. 97-99) writes:

"In preparing this book effort was made to prepare a chapter setting forth the creative years of women only. But the attempt to find sufficient data for the construction of separate age-curves in specific fields of endeavour, especially in scientific fields, was rather unrewarding . . . so few women have contributed greatly to the several sciences." . . . "Eventually, by selecting from each of a number of different scientific fields the names of the few creative women for whom birth and death rates were available, it was possible to construct a curve revealing women's most creative years in science." . . . "On the whole the creative years of women do not differ greatly from the creative years of men."

This conclusion, although probably true, is much less firmly based than some of his other conclusions.

Lehman (p. 328) also argues that:

"A decline occurs prior to 40 in physical vigor, energy, and resistance to fatigue. This decline is probably far more important than such normal age changes as may occur in adult intelligence prior to outright senility."

And (p. 36):

"It may well be that future generations will not take seriously many of the present-day attempts to measure the 'intelligence' of adults of widely varying ages."

However, if vigor and opportunity and the many other non-intellectual factors that Lehman mentions are more important than intelligence in the creative thinking of adults, then it seems to follow that quantity rather than quality of output should be affected by age; Lehman's data clearly do not support such an idea, therefore his conclusions are questionable.

This is not the place to embark upon a thorough exposition and criticism of Lehman's, "Age and Achievement." Fortunately, criticisms would be few for the book is a model of patient and cautious scientific exploration. Lehman has given us fresh insights into the relationships between age and creative output; his basic findings indeed provide the necessary factual foundation upon

which we can build our knowledge of the adult intellect, while his more speculative conclusions provide a useful theoretic framework within which experimental studies can be designed. Experimental studies in this field are useful for a number of reasons: 1) they act as checks on Lehman's basic conclusions, or 2) the facts which Lehman has established under very different circumstances can be used as criteria for the validity of their methods and results; 3) they can test Lehman's speculative conclusions—perhaps more rigorously; and 4) they can test hypotheses which are relevant to Lehman's conclusions but not amenable to his methods.

TEST MATERIAL

This report outlines some experimental investigations of the effects of age on creative intellectual output, in which a special test of creative thinking was used (the Shaw Test) first publicized by Howson (3) in 1948, and adapted by the present author for use in his studies of the effects of age on intellectual processes. The version used in this inquiry* consists of 4 wooden blocks which can be arranged in 15 different series: according to height, weight, position of notch, etc.

In addition to the 15 normal, abstract, and clearly defined sequences (which are called Grade A responses), there are at least 41 less frequent or less clearly defined sequences (which are called Grade B responses), e.g., the volume of the blocks and the positional relation between the word and the notch. There are at least 16 Grade C responses, mostly illogical, confused, and concrete, e.g., making patterns with the blocks, and grouping the blocks instead of serializing them. Finally, there are at least 5 Grade D responses, the poorest, mostly failures of comprehension, and inane responses, e.g., building towers with the blocks and simply describing the blocks.

This classification of responses was made through an objective item-analysis of the test performances of 256 relatively normal adults of varying ages. No time limit was imposed and the subjects were, in a sense, tested to the limits of their capacity for producing ideas. The general significance of the Shaw Test responses is that good and fairly good (A and B) ones indicate the speed, power, originality, and general efficiency of the subject's thinking; while the fairly poor and poor (C and D) ones seem to indicate the abnormality, defectiveness, or degree of deterioration of the subject's thinking. A reliability coefficient for the Grade A responses, computed by the method of rational equivalence (5) came to 0.87. The product-moment r between Grade A responses and the Wechsler-Bellevue Efficiency Quotient was +0.745 (+0.641 with age held constant); the r between Grade D responses and WBEQ was −0.505 (−0.303 with age held constant).

It can be provisionally assumed that the Shaw Test is a rough measure of creative intellectual output, since it seems to involve: 1) the imaginative exploration of the possibilities of a given situation within and sometimes beyond a given set of rules and assumptions; 2) the mental operations of abstracting, serializing and productive thinking; and 3) the personal qualities of persistence, flexibility, originality, and fluency. This is of course an estimate of the test's face-validity, and we cannot say anything definite about what the Shaw Test is measuring until additional validation studies have been done. The author has, however, established that the test is measuring some kind of fluid ability; the following quotation from Cattell (1, p. 178) will make this point clear:

> "Fluid ability has the character of a purely general ability to discriminate and perceive relations between any fundaments new or old. It increases until adolescence and then slowly declines. It is associated with the action of the whole cortex. It is responsible for the intercorrelations, or general factor, found among children's tests and among the speeded or adaptation-requiring tests for adults." . . . "Crystallized ability consists of discriminatory habits long-established in a particular field originally through the operation of fluid ability, but no longer requiring insightful perception for their successful operation." . . . "Intelligence tests test at all ages the combined resultants of fluid and crystallized ability, but in childhood the first is predominant whereas in adult life, owing to the recession of fluid ability, the peaks of performance are determined more by crystallized abilities."

There is obviously an important connection between fluid ability and creative intellectual achievements of all kinds, e.g., the development of skills, concepts, and insights.

*Full description, details, and photographs of the Shaw Test can be obtained from this author. Residents in the United Kingdom can borrow a copy of the test for short periods. The author will be glad to enter into correspondence with anyone interested in the test, which is adaptable to a variety of uses.

PROBLEMS AND HYPOTHESES

There are two questions:

(A) Can we, by an experiment involving the use of a special test of creative intellectual output, i.e., the Shaw Test, obtain results compatible with those satisfactorily established by Lehman?

(B) Can we, by the same method, raise additional evidence on issues not satisfactorily settled by Lehman?

A number of working hypotheses, based on Lehman's findings and relevant to these questions, should forecast the effects of age on Shaw Test performance:

A^1. Quantity of output declines slowly.

A^2. Quality of output declines faster than quantity.

A^3. The peak years for both quality and quantity of output occur in the youngest age-group (Mean age = 27 years).

A^4. Output of very high quality declines faster than output of lesser merit.

B^1. Quality and quantity of output are positively and significantly associated.

B^2. No sex differences exist in connection with any association between age and creative intellectual output.

B^3. The decline with age of quantity and quality of output is not associated with the decline with age of general intelligence.

In this report it will be argued that if the Shaw Test performance of adults varies with age in the same way as creative achievement, using Lehman's firmly established conclusions for comparison, then the two are probably related. Such a finding would serve as indirect evidence of the validity of the Shaw Test as a measure of creative intellectual output and would justify the use of the test in additional studies of problems not satisfactorily settled by Lehman.

METHOD

The subjects taking part in the experiment were volunteers recruited from among friends, acquaintances, casual contacts, local industries, churches, staffs of institutions, social clubs, and centers of adult education. An attempt was made to establish comparable groups at each of 4 age-levels: 17-35, 35-51, 51-66, and 66-82 years of age (CA refers to chronological age); in each age-group there were 32 men and 32 women, making a grand total of 256 subjects. The subjects were of average to superior intelligence and social background, although the subjects in the fourth age-group were slightly inferior in these respects. Intelligence quotients (IQ) and efficiency quotients (EQ) were obtained from 11 subtests of Form I of the Wechsler-Bellevue Intelligence Scale for Adults (WB) as described by Wechsler (8); slight modifications on some items were introduced to suit the English culture pattern. The ratings for social background were based on educational and occupational history and ranged from 1 (relatively good) to 5 (relatively poor).

Table 1 gives details of the population.

The Shaw Test instructions to subjects were as follows:

"Pick up each of these four blocks and examine them." (Pause) "You will see that they can be arranged in a kind of a logical order from left to right; they can be arranged in a sequence, in a series. There are a number of ways of arranging them; can you find just one way to begin with?

If subjects proceeded without difficulty, then they were asked to find as many different ways of arranging the blocks as possible. No time limit was imposed, but when subjects said that they were unable to find any more series they were told to pick up the blocks again and examine them individually; this was to give them a further opportunity to react to the weight stimulus. The time taken usually varied between 10 and 15 minutes. Subjects were encouraged to go on finding as many different sequences as they could. If a subject found difficulty in understanding the test instructions or could not find a sequence, then the alphabetic sequence was demonstrated and explained to him; if he could not continue, then the height sequence was demonstrated and explained; subjects were asked to repeat the demonstrations, and their successes or failures were recorded. When no further responses were forthcoming after an interval of repeated instructions and encouragement, the test was regarded as complete.

RESULTS AND INTERPRETATIONS

The quantity of output on the Shaw Test is defined by the total number of responses regardless of quality. The quality of output is defined in two ways: 1) in terms of Grades A, B, C, or D, which are respectively good

TABLE I. DESCRIPTION OF THE POPULATION IN TERMS OF AGE, SEX, SOCIAL BACKGROUND, AND WECHSLER-BELLEVUE IQ.; 32 MEN AND 32 WOMEN IN EACH AGE GROUP.

Age Group	I (17-35 Yrs.)	II (35-51 Yrs.)	III (51-66 Yrs.)	IV (66-82 Yrs.)	All Age Groups (17-82 Yrs.)
Men, mean age	27.31	42.47	57.56	71.75	49.77
Men, SD age	5.43	4.20	4.89	4.02	17.26
Women, mean age	26.09	44.81	58.81	71.88	50.40
Women, SD age	5.02	4.24	4.89	4.12	17.58
Both, mean age	26.70	43.64	58.19	71.81	50.09
Both, SD age	5.27	4.37	4.89	4.16	17.41
Men, mean social background	2.94	2.72	2.56	2.69	2.73
Men, SD social background	0.78	1.09	1.00	1.04	0.99
Women, mean social background	2.97	3.00	3.13	3.16	3.06
Women, SD social background	0.81	0.90	1.01	1.08	0.97
Both, mean social background	2.95	2.86	2.84	2.92	2.89
Both, SD social background	0.81	1.01	1.06	1.10	1.01
Men, mean WBIQ	122.69	127.34	127.03	121.31	124.59
Men, SD WBIQ	8.31	8.31	8.42	11.05	9.46
Women, mean WBIQ	119.03	119.63	116.03	110.56	116.31
Women, SD WBIQ	9.03	10.25	11.75	13.15	11.75
Both, mean WBIQ	120.86	123.48	121.53	115.94	120.45
Both, SD WBIQ	8.87	10.16	11.61	13.24	11.46

fairly good, fairly poor, or poor; and 2) in terms of popular, i.e., frequently occurring A responses, and original, i.e., infrequently occurring A responses, referred to as Ap and Ao respectively. The reason for this dual definition is that in 1) a very wide range of quality in creative intellectual performance is covered, and in 2) a rough approximation is made to Lehman's data, which refer to high-grade and very high-grade performance.

The totals, means, and SDs of scores of the various classes of Shaw Test response for each age-group are given in table 2.

The contingency coefficient computed from table 2 = 0.317 (corrected for broad categories = 0.366); the SD of C = 0.019. The obtained C is nearly 17 times the SD of C; there is therefore a significant relationship between the over-all quality of Shaw Test performance and age; inspection of table 2 shows that the relationship is negative, i.e., the quality of creative intellectual output declines with age.

TABLE 2. RESPONSES TO THE SHAW TEST IN TERMS OF GRADE AND AGE GROUP.

Age Group	I (17-35 Yrs.)	II (35-51 Yrs.)	III (51-66 Yrs.)	IV (66-82 Yrs.)	Total (17-82 Yrs.)
Total A	586	488	417	235	1726
Mean	9.2	7.6	6.5	3.7	6.7
SD	2.8	3.7	3.7	3.1	3.9
Total B	129	76	83	67	355
Mean	2.0	1.2	1.3	1.0	1.4
SD	2.7	1.3	1.8	1.3	1.9
Total C	80	98	140	148	466
Mean	1.2	1.5	2.2	2.3	1.8
SD	1.6	1.8	2.3	1.9	1.9
Total D	25	52	91	163	331
Mean	0.4	0.8	1.4	2.5	1.3
SD	0.7	1.3	1.2	1.7	1.5
Total ABCD	820	714	731	613	2878
Mean	12.8	11.2	11.4	9.6	11.2
SD	4.4	3.5	5.2	3.9	4.4

It is clear that there are distinct changes with age in the character and quality of creative intellectual output. The trend is consistent, and from age-group 1, which includes the peak years for both quantity and quality of achievement, there is a noticeable drop in good quality output (Grade A) and an increase in poor quality output (Grade D); the trend is reinforced by losses and gains with age in fairly good (Grade B) and fairly poor (Grade C) output, respectively.*

The results given in table 2 are supported by the fact that

r A × CA = −0.524 and r D × CA = +0.530

and we can conclude that normal decline with age on the Shaw Test is not only a gradual loss of intellectual power, i.e., output or creativity, but also a complex pattern of changes in which a rapid decrease in the production of good (A and B) ideas, i.e., ideas which are fairly clear, abstract, logical, and perhaps original, is rather inadequately compensated for by an increase in poor (C and D) ideas, i.e., ideas which are concrete, illogical, inaccurate, confused, and bizarre. Weisenberg, Roe, and McBride (9) (preface) reported that normal people give a percentage of abnormal responses on Head's tests of aphasia and kindred disorders of speech. In this inquiry we have confirmed experimentally what the clinician has always known, i.e., that the borderline between normal and abnormal thinking is not always clear-cut, and that the normal person, particularly the normal aged person, under stress will give abnormal responses.

Table 2 shows that the quality of Shaw Test performance (Grade A responses) falls off with age more quickly than quantity of performance (total responses); moreover

r A × CA =−0.524 and r Total × CA =−0.252.

The difference between these two rs is significant only between the 0.1 and 0.2 levels of confidence, but it is sufficient for us to suppose that the quality of creative intellectual output is more closely associated with age than is mere quantity.

*The various effects of age on creative intellectual output as revealed by the Shaw Test performances of these subjects can be vividly illustrated by graphic and pictorial methods, but this is less accurate and adds no further essential information, and the data will be presented in tabular form only. Graphs and "pie-charts" based on these Shaw Test results can be used very effectively in the classroom to illustrate changes with age in adult intelligence (Cf. 6 p. 4-7).

The 15 good quality Shaw Test responses can be divided into 2 classes: the 7 most frequently occurring A responses (Ap), and the 8 less frequently occurring A responses (Ao). The Rorschach Technique (4, p. 181-182, and 216-217) uses a similar classification of responses into popular and original, and gives them a significance that could well be applied to Shaw Test responses: popular responses indicate a degree of normal activity and conformity, whereas original responses indicate a certain degree of brilliance, specialization, or creativity. There are many qualifications to this rule, and the comparison will not be pressed further at this stage.

The relationships between age and popularity or originality of Shaw Test response can be seen in table 3:

TABLE 3. POPULAR AND ORIGINAL GRADE A SHAW TEST RESPONSES IN EACH AGE GROUP.

Age Group	I (17-35 Yrs.)	II (35-51 Yrs.)	III (51-66 Yrs.)	IV (66-82 Yrs.)	Total (17-82 Yrs.)
Total Ap...	376	324	299	185	1184
Mean...	5.9	5.1	4.7	2.9	4.6
SD.....	1.3	1.8	2.0	2.2	2.1
Total Ao...	210	164	118	50	542
Mean...	3.3	2.6	1.8	0.8	2.1
SD.....	1.9	2.3	2.2	1.3	2.2
Total A....	586	488	417	235	1726
Mean...	9.2	7.6	6.5	3.7	6.7
SD.....	2.8	3.7	3.7	3.1	3.9

Chi-square computed from table 3 = 18.9980, $P < 0.01$; this finding supports the notion that Shaw Test achievements of greater and lesser merit do not decline with age at the same rate, and there is a clear tendency for superior (original) ideas to decline more rapidly with age than ideas of lesser merit (popular ideas). Moreover

r Ap × Age = −0.527 whereas
r Ao × Age = −0.690

so that originality is significantly more closely associated with age than unoriginal thinking.

So far it has been found that the relationships between age and creative intellectual output on the Shaw Test are exactly what had

been predicted, i.e., the peak years for both quality and quantity of output occur in the youngest age-group (mean age, 27 years); quantity of output declines gradually with age, whereas quality of output declines more rapidly; output of very high quality (Ao) declines faster than output of lesser merit (Ap). Hypotheses A^1, A^2, A^3 and A^4 are all supported by the experimental evidence; so that the answer to the first question (A) is that we can, in fact, by an experiment involving the use of a special test of creative output, i.e., the Shaw Test, obtain results compatible with those firmly established by Lehman in quite a different context. This finding is indirect evidence in support of the argument that performance on the Shaw Test is related to creative intellectual output and that the methods and results obtained in this experiment are valid.

The next part of the investigation tests three of Lehman's less firmly established conclusions, and begins with an examination of the relationships between quality and quantity of intellectual output. The relationship between popular and original responses on the Shaw Test is shown by

$$r\ Ap \times Ao = +0.674$$
$$(+0.576 \text{ with age held constant})$$

This means that, in general, people who produce more original ideas also tend to produce more ordinary ideas, i.e., that quality and quantity of output are fairly closely associated. But this association only holds when the output under consideration is above a certain minimum level of quality. If we examine the association between superior and inferior Shaw Test performance then

$$r\ A \times D = -0.610$$
$$(-0.462 \text{ with age held constant})$$

moreover

$$r\ A \times WBEQ = +0.745$$
$$(+0.640 \text{ with age held constant})$$

and

$$r\ D \times WBEQ = -0.505$$
$$(-0.303 \text{ with age held constant});$$

these correlations may be interpreted as meaning that the high-grade intellect tends to exclude from action and possibly from consciousness those forms of thought that are called primitive (10); i.e., inane, bizarre, confused, and concrete forms of thought. The correlations between inferior forms of response and age

$$r\ D \times CA = +0.530$$
$$(+0.343 \text{ with WBEQ held constant})$$

and between intellectual efficiency and age

$$r\ WBEQ \times CA = -0.561$$

demonstrate that as the intellect weakens, perhaps because it weakens, the more primitive forms of cognition come increasingly into play. The increase with age of inferior intellectual responses may be seen as a *compensatory device* designed to offset the effects of normal deterioration; however, an alternative explanation has been indirectly offered by Dennis and Mallinger (2), since they claim to have found evidence of a *regression* in old age to animistic and subconceptual modes of thought. The emergence of primitive inferior intellectual processes is partly but not entirely a function of the absolute level of intellectual efficiency and is to some extent a function of relative decline, since r D × WBEQ with age held constant and r D × CA with WBEQ held constant are significantly different from zero.

Rashkis (7) in another connection has shown that intellectual performance can be usefully classified into two parts: performance potentialities, i.e., intelligence and knowledge, and performance evaluation, i.e., self-criticism. The intellectual behavior of individuals with general paresis and cerebral arteriosclerosis is mainly because of impaired performance potentialities; however, in subjects with arteriosclerosis the capacity for performance evaluation continues to function, whereas in those with general paresis it is greatly impaired. In schizophrenia, performance evaluation continues to function but in a deviant way. The exercise of discretion and self-criticism was frequently observed during the present inquiry, e.g.,

"I could have put them in order of the size of the animals, but that would depart from the intrinsic properties of the blocks." "I could build a tower, but I don't suppose you want that do you?" "I could put them in order of the amount of bevel on the edge, but that is stupid, I am imagining things."

It is arguable that performance evaluation is as important as performance potential in effective thinking and that it is the *balance* of creative (potential) and critical (evaluative) forms of thought that makes sane productive thinking possible and constitutes the core of scientific method.

The necessary conclusions to be drawn from the results so far are that (1) the gradual decline with age of total intellectual output represents a loss of drive, persistence, imagination, perceptual acuity, or a combination of these and other factors; (2) the very rapid decline with age of good quality output represents a loss of performance potentialities and especially a recession of fluid ability; (3) the increase with age of poor quality, confused, bizarre, and other primitive forms of response represents partly an impairment of the self-critical attitude, i.e., a loss of performance evaluation, partly a compensatory process designed to offset the effects of normal intellectual deterioration, or partly a regression to primitive modes of thought.

There are some consistent sex differences in general intelligence (table 1) which the author believes are not entirely because of sampling errors, and there are some slight but inconsistent sex differences in Shaw Test performance when general intelligence is held constant. Neither of these factors however in any way influences the general conclusions about the effects of age on the intellectual output of men and women, and they will not be elaborated upon in this report.

Equal groups of men and women were selected at a constant WBIQ level in each age group; the Shaw Test results of these matched groups are given in table 4. The data support the following points, clearly visible when percentage graphs are drawn, that 1) although the Shaw Test total score seems to decline with age less rapidly for women than for men, the difference is slight; moreover, the difference between men and women for r Total × CA (−0.224 and −0.293, respectively) is not significant; 2) although the Shaw Test Grade A score seems to decline faster for women than for men, the trend is not consistent; moreover, the difference between r A × CA (−0.485 and −0.580, respectively) is not significant. The degree of association therefore between age and quantity and between age and quality of intellectual output is much the same for both sexes. In addition, the peak years for both quantity and quality of output are the same for both sexes.

The same procedure can be used to test for sex-differences in the effects of age on popular and original responses; the Shaw Test

TABLE 4. SHAW TEST RESPONSES FOR 16 MEN AND 16 WOMEN IN EACH AGE GROUP HAVING A MEAN WBIQ OF 121.63.

Age Group	I (17-35 Yrs.)	II (35-51 Yrs.)	III (51-66 Yrs.)	IV (66-82 Yrs.)
All Responses				
Men, total ABCD...	194	169	160	155
Women, total ABCD	198	174	189	172
$X^2 = 1.2653$, $P > 0.05$				
Grade A Responses				
Men, total A.....	127	113	85	59
Women, total A....	169	108	108	81
$X^2 = 4.4102$, $P > 0.05$				
Popular Responses				
Men, total Ap.....	84	79	67	47
Women, total Ap...	105	80	84	66
$X^2 = 1.9375$, $P > 0.05$				
Original Responses				
Men, total Ao.....	43	34	18	12
Women, total Ao...	64	28	24	15
$X^2 = 3.4866$, $P > 0.05$				

results of the matched groups of men and women are given in table 4. The data demonstrate that the degree of association between age and intellectual output of greater and lesser merit is much the same for both sexes; moreover, the difference between r Ap × CA for men and women (−0.481 and −0.557, respectively) is not significant; the difference between r Ao × CA for men and women (−0.363 and −0.477, respectively) is not significant; the difference between r Ap × Ao for men and women (+0.614 and +0.642, respectively) is not significant. Hence, it is

concluded that age influences the intellectual originality of men and women to much the same extent, and that in both sexes, within normal limits, quality and quantity of output are associated to much the same degree.

In real life of course a variety of factors influence the intellectual achievements of men and women, and all that is claimed in this report is that the experimental evidence seems to support the notion that it is not lack of intellectual creative capacity as such that prevents women from being the equals of men in intellectual creative achievement.

The final problem is to discover the relationships between general intelligence and creative output; the relevant results are

r Total × CA = −0.252
r Total × CA (with WBEQ held constant) = +0.079
r A × CA = −0.524
r A × CA (with WBEQ held constant) = −0.192
(For N = 256, a two-variable coefficient of correlation of 0.163, and a three-variable coefficient of correlation of 0.191 are significant at the 0.01 level)

We can conclude from these figures that although the loss with age of general intellectual efficiency does not entirely account for the decline in quantity and quality of creative output, it does account for the major part.

The answer to the second question (B) is that we can, by an experiment using a special test of creative intellectual output, raise additional evidence on issues not satisfactorily settled by Lehman. Hypotheses B^1 and B^2 are supported, since quantity and quality of creative output are found to be positively and significantly related, and no significant sex differences are found in connection with any association between age and creative output. Hypothesis B^3 is refuted, since the decline with age in quality and quantity of creative output is strongly associated with the normal decline with age of general intelligence.

SUMMARY

Lehman's work was used as a framework of fact and theory within which an experiment was designed to see whether performance on the Shaw Test, a test of creative intellectual output, varied with age in the same way as actual achievement varies with age as decribed by Lehman.

The test was administered to 4 comparable groups of men and women varying in age, and the results conformed fairly well to expectations based on Lehman's analysis. The results of the first part of the experiment showed that the peak years for both quantity and quality of output occur in the youngest age group (Mean age = 27 years); both quantity and quality decline with age but quality declines the more rapidly; output of very high quality declines faster than output of lesser merit. These results were taken as evidence in favor of the view that Shaw Test performance is closely linked with creative intellectual capacities.

The second part of the experiment analyzed the results further in order to raise additional evidence on issues not satisfactorily settled by Lehman. The results confirmed Lehman's conclusion that the original thinker is more productive of ideas in general, but only if the ideas are above a certain minimum level of quality; it was found that the high-grade intellect tends to exclude primitive and bizarre ideas. When general intelligence was held constant, no sex differences seemed to exist in connection with any association between age and creative output. One result failed to conform to the predictions based on Lehman's analysis: the effect of holding intelligence constant is to reduce considerably the apparent association between age and quantity and age and quality of output.

Although loss of intellectual efficiency with age does not entirely account for the decline in quantity and quality of creative output, it does account for the major part; hence, contrary to Lehman's argument, the decline of adult intelligence is a potent factor in the reduction with age of creative intellectual output. On the whole, the experimental evidence supports the view that the Shaw Test performance is closely related to intellectual creativity and supports several but not all of Lehman's conclusions.

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OCCURRENCE OF RESISTANT *STAPHYLOCCOCI* IN AN INSTITUTION FOR THE AGED IN COPENHAGEN

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IT IS GENERALLY agreed that the incidence of bacterial strains resistant to the routine chemo-therapeutics and antibiotics will increase. Growth conditions of such strains may be favored through the restraining effect of the therapy on the competitive normal bacterial flora. In hospitals such resistant strains will probably accumulate and be transferred from staff members and chronic patients to the newly admitted patients. It was therefore decided to investigate the extent to which such increase was reflected in an institution where the rotation of patients is slight. De Gamles By was selected for the study because the discharge of patients from this institution is rare, the great majority of the patients remaining in De Gamles By until their death. The hospital division of the institution is dominated by chronic patients admitted for nursing care only. Infections, mostly pneumonia and pyelitis, occur occasionally and are always treated with the routine chemo-therapeutics and antibiotics. A hospital of this nature might be presumed to be infested to an increasing degree with resistant bacteria and in this respect should range high among hospitals.

A certain number of penicillin resistant *staphylococci* occur among the natural *staphylococci* and their occurrence is increased in the nose and throat of patients after penicillin treatments. Böe and Vogelsang (1) examined 445 patients and found 15.5 per cent of the pathogenic *staphylococci* in the throat to be penicillin resistant even before the treatment had been instituted; 68.1 per cent became resistant after treatment.

Several authors point out that hospital staff members more frequently are carriers of penicillin resistant *staphylococci* than the general population. Rountree and Thomson (8) compared 200 members of hospital staffs with 200 blood donors and found 32 per cent of the former group to be nasal carriers of penicillin resistant *staphylococci* as compared to 4 per cent in the latter group. Rountree and Barbour (7) showed clearly how student nurses to increasing degrees become carriers of penicillin resistant *staphylococci* during their term in hospital. Before entering the hospital nasal *Staph. aurei* were found in 52.6 per cent, 4.3 per cent of which proved penicillin resistant. Five weeks later 71.4 per cent of the students were carriers of *staphylococci*, 32.1 per cent of which were resistant to penicillin. Several authors (3, 6, 9, 10, 11, 12) have confirmed these findings. Finally Dowling and associates (2) showed that patients carry the resistant bacteria into the general population when they are discharged from the hospital.

EXPERIMENTAL

The object of this investigation was to evaluate the occurrence of *staphylococci* during the spring and summer of 1954 in De Gamles By, a social institution to which old men and women are admitted to receive medical and custodial care. Previous to admission they go to the hospital for a medical examination; their case record is prepared, and after a period of observation it is decided whether they should go to the department for healthy old people or whether their condition requires permanent treatment in the hospital proper.

MATERIAL

The investigation included 43 healthy old persons, 61 patients suffering from various ailments, and 27 members of the staff. The healthy inhabitants each had their private room in the institution, whereas the patients were admitted to wards with 2 to 10 patients in each ward. The staff included physicians, day nurses, and night nurses.

Swabs from nose and throat were taken from 26 of the patients; nasal *Staph. aurei* or *Staph. albi* were found in all of them, but only 11 patients exhibited *staphylococci* in the throat. Nasal *Staph. aurei* were isolated from 19 patients and nasal *Staph. albi* from 20; only 9 and 5, respectively, were isolated from the throat. Thus, *staphylococci* were far more frequent in the nose than in the throat, for which reason swabs were taken only from the noses of the remaining patients.

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If penicillin resistant *staphylococci* were not encountered on the first occasion a second swab was taken. The findings reported in this study represent the final results from the examination. The demonstration of the presence of *staphylococci* has been the central point in this work. The examination included *Staph. aureus* as well as *albus* because the latter may prove pathogenic. Some nasal, non-hemolytic *streptococci* and a few *gram-positive rods* were found; hemolytic *streptococci, pneumococci,* and *gram-negative rods,* however, were only occasional occurrences.

Concurrently with the examination of nasal swabs, *staphylococci* were isolated from 10 of the private rooms inhabited by healthy old people and from 10 hospital wards. The cultures were isolated from floors, tables, radiators, and doorknobs, or 10 per cent blood agar plates were placed in the rooms and wards for 24 hours. The procedure was either to take 5 cultures from the room or to place 5 plates there.

TECHNIQUE

Nasal swabs were taken in the morning and the swab stick sent in a sterile test-tube to the State Serum Institute where it was moistened with serum broth and plated onto 10 per cent blood agar plates. The disseminated material was spread by means of a loop. Subsequently the swab stick was inserted into a glass with 5 per cent serum broth and incubated together with the plate at 37 C. for 18 to 20 hours. The serum broth culture was plated onto a blood agar plate and bacteria from the latter compared with those from the original plate.

If possible, two yellow and two white *staphylococci* cultures were isolated from the individual swabs. The sensitivity was determined on the individual strains. The colonies were isolated from the original culture on the blood agar. Only when it was impossible to isolate a sufficient number of colonies was material supplied from the blood agar plate derived from the original serum broth inoculation. If possible, five yellow and 5 white *staphylococcus* cultures were isolated from the furniture in the rooms and from the exposed blood agar plates; the sensitivity of each group of cultures was determined on mixtures of the white or yellow colonies.

The cultures taken from the furniture were handled exactly like the nasal swabs. The blood agar plates were closed after 24 hours and incubated until the following day.

The isolated *staphylococci* were cultured in mannite and citrate-plasma. Only when both reactions were positive were the strains labelled *Staph. aureus;* when both reactions were negative the strains were labelled *Staph. albus.* If one reaction was positive, the other negative, the strains were not labelled *staphylococcus.*

The sensitivity test was performed by the tablet method on 10 per cent peptone-free blood agar (4, 5). The reaction was tested toward 9 different preparations (8 antibiotics and 1 sulfa preparation): penicillin, streptomycin, aureomycin, chloromycetin, terramycin, bacitracin, neomycin, erythromycin, and sulfathiazol, the latter as representative for the sulfa drugs. The material disseminated on the plates consisted of the aforementioned bacteria suspended in buffered saline. Primarily the *staphylococci* were diluted to standard 1:5, i.e., diluted 5 times higher than a 24 hour broth culture of the standard *Staph. aureus* strain 209 P (F.D.A.); one loopful (2 mm.) of the dilution was transferred to 2 ml. saline and 1 loopful of the suspension was spread on the plate with a bent glass rod. The blood plates were large, the diameter measuring 14 cm., accommodating 9 tablets; 7 of these were arranged within the circumference and 2 in the center; when the tablets were placed on the inoculated plates these were incubated at 37 C. until the following day. The zones of inhibition were read in millimeters and the degree of sensitivity estimated according to the following scale:

+++ $\geqq$ 25 mm. = sensitive.
++ 23-24 mm. = medium sensitive.
+ 16-22 mm. = relatively resistant.
0 $\leqq$ 15 mm. = resistant.

The sensitivity tablets applied for these examinations were of the following concentration per tablet: penicillin, 25 international units; streptomycin, 3 mg.; aureomycin, 1 mg.; chloromycetin, 1 mg.; terramycin, 1 mg.; bacitracin, 500 units; neomycin, 1000 units; erythromycin, 500 micrograms; sulfathiazol, 10 mg.

RESULTS

A. *Determination of staphylococci in subjects.*—Five nasal *Staph. aurei* and 5 nasal *Staph. albi* were isolated from each of two subjects. The sensitivity to all 9 drugs was determined separately for all 20 strains. In the first subject the 5 *Staph. aureus* colonies were found sensitive to all 9 drugs; the 5 *Staph. albus* colonies were all resistant to penicillin and sulfathiazol but sensitive to the rest of the drugs. Conditions in the second subject were more complicated. Three of the 5 *Staph. aurei* were resistant and 2 were sensitive to penicillin. All the other strains were sensitive to the rest of the drugs. One among the 5 *Staph. albus* colonies was resistant to penicillin and sulfathiazol but sensitive to the rest; the 4 remaining strains were sensitive to all 9 drugs.

Hence it will be seen that penicillin resistant and penicillin sensitive *Staph. aureus* as well as *Staph. albus* strains may be encountered in the same patient. Isolation of 4 colonies from a patient is therefore no guaranty that all species of the *staphylococci* have been located. If penicillin resistant strains were not isolated on the first occasion the swabbing was repeated and another 4 colonies of *staphylococci* isolated. An examination of 8 colonies from one subject should guarantee the isolation of the penicillin resistant *staphylococci*, if any. The penicillin sensitivity of the strains has been the focal point of the examination, since penicillin is the drug applied most frequently in the routine treatment of the patients in De Gamles By.

TABLE 1. OCCURRENCE OF NASAL *Staphylococci* IN 131 HEALTHY SUBJECTS, PATIENTS, AND STAFF IN DE GAMLES BY.

Group	No. Examined	No. with *Staph. aureus* (%)	No. with *Staph. albus* (%)
Healthy subjects	43	37	91
Patients	61	67	85
Staff	27	52	100

Table 1 records the percentage of subjects examined with nasal staphylococci. The figures are as follows: healthy subjects with *Staph. aurei*, 37 per cent; patients, 67 per cent; staff, 52 per cent. The majority of the 131 subjects examined exhibited nasal *Staph. albus:* healthy subjects, 91 per cent; patients, 85 per cent; staff, 100 per cent.

Table 2 records the number of resistant *Staph. aureus* and *Staph. albus* strains encountered in the 3 groups and specifies the sensitivity to all 9 drugs. The number of subjects with nasal Staph. aureus is stated. Subjects with nasal, resistant *Staph. aureus* are recorded in percentage of the total number of subjects examined from the group. Bold face figures give the number of carriers of resistant strains in percentage of the carriers of nasal *Staph. aureus.*

Among the patients 54 per cent were carriers of nasal penicillin resistant *Staph. aureus;* among the staff, 37 per cent; but only 12 per cent among the healthy old people. Sulfathiazol resistance exhibits similar figures: the patients, 25 per cent; the staff, 15 per cent; but only 7 per cent among the healthy subjects. Resistance to streptomycin, aureomycin, chloromycetin, and terramycin reads as follows: among the patients 10, 2, 3, and 2 per cent, whereas all *Staph. aurei* both from staff and healthy subjects proved sensitive to the above 4 antibiotics. All the *Staph. aurei* from the 3 groups proved sensitive to the 3 most recent antibiotics, bacitracin, neomycin, and erythromycin.

The highest number of penicillin resistant *Staph. albi* was encountered in members of the staff (74 per cent). The patients exhibited 62 per cent and the healthy subjects 19 per cent. Likewise, sulfa resistant *Staph. albi* were most frequent in the staff (30 per cent), whereas the patients exhibited 23 per cent and the healthy subjects 9 per cent.

Streptomycin resistant *Staph. albi* were not encountered among the healthy subjects but were found in 7 per cent of the staff and in 3 per cent of the patients. Aureomycin and terramycin resistant strains were manifest in all 3 groups, but also most abundantly in the staff (11 per cent), less abundant in the patients (7 per cent) and least frequent in the healthy subjects (4 per cent). Chloromycetin resistant *Staph. albi* were not encountered among the healthy but in 7 to 8 per cent of the members of the staff and the patients. All

TABLE 2. OCCURRENCE OF RESISTANT NASAL *Staph. Aureus* AND *Staph. Albus* STRAINS IN 131 HEALTHY SUBJECTS, PATIENTS, AND STAFF IN DE GAMLES BY.

Group	No. Examined	No. with Nasal *Staph.*	Percentage* of Subjects with Strains Resistant to: Penicillin	Sulfathiazol	Streptomycin	Aureomycin	Chloromycetin	Terramycin	Bacitracin+ Neomycin+ Erythromycin
Staph. aureus									
Healthy subjects	43	16	12 **31**	7 **44**	0 **0**	0 **0**	0 **0**	0 **0**	0 **0**
Patients	61	41	54 **80**	25 **37**	10 **15**	2 **3**	3 **5**	2 **3**	0 **0**
Staff	27	14	37 **71**	15 **29**	0 **0**	0 **0**	0 **0**	0 **0**	0 **0**
Staph. albus									
Healthy subjects	43	39	19 **21**	9 **10**	0 **0**	4 **5**	0 **0**	4 **5**	0 **0**
Patients	61	52	62 **73**	23 **27**	3 **4**	7 **8**	8 **10**	7 **8**	0 **0**
Staff	27	27	74 **74**	30 **30**	7 **7**	11 **11**	7 **7**	11 **11**	0 **0**

*Roman figures indicate number of subjects with resistant nasal *Staphylococci* strains in percentage of the total number of subjects examined within the various groups.

Bold face figures indicate number of subjects with resistant strains in percentage of the number of subjects included in the group with nasal *Staphylococci* (sensitive or resistant).

the examined *Staph. albus* strains proved sensitive to bacitracin, neomycin, and erythromycin.

Examination disclosed no difference in the occurrence of nasal *Staph. aurei* in patients admitted to small wards (2 or 3 beds) and those admitted to larger wards (5, 6, or 10 beds).

B. Determination of staphylococci in wards and private rooms of the institution.—It has been mentioned that 5 cultures were taken or 5 blood agar plates were placed in the individual wards and private rooms inhabited by healthy old people, a total of 10 rooms of each classification. Up to 10 colonies, 5 yellow and 5 white, if possible, were isolated from each test, i.e., about 50 strains from each room. For the sake of convenience the sensitivity was not determined on the individual strains but on culture mixtures. When 5 yellow and 5 white colonies had been isolated from a certain room, 2 sensitivity tests were performed: 1 on a mixture of yellow and 1 on a mixture of white strains. Thus the *Staph. aurei* were kept apart from the *Staph. albi*.

The occurrence in such mixture of a single resistant strain suffices to show the entire mixture resistant. Hence the technique opens no possibility of deciding whether the resistance determined was due to one or more resistant strains.

The findings are therefore recorded by two figures: 1) the lowest number permissible, i.e., one resistant strain in the mixture, and 2) the highest number, i.e., all the strains included in the mixture. Example: The figures 2 to 9 (cf. table 3) indicate that two sensitivity tests with resistant results have been carried out; 9 strains were included in these tests. In this example the number of resistant strains will range between 2 (1 in each mixture) and 9 (all strains in the mixture).

Since findings from cultures taken from furniture and from blood agar plates were in accord they were recorded as one item (table 3).

Table 3 records the number of resistant *Staph. aurei* as well as *Staph. albi* isolated from wards and private rooms. The table includes, as already mentioned, the lowest

TABLE 3. OCCURRENCE OF RESISTANT *Staphylococci* COLONIES IN PRIVATE ROOMS AND WARDS FOR HEALTHY SUBJECTS.

Average from 10 rooms for:	No. of Colonies Examined	No. of Colonies Resistant to: Penicillin	Sulfathiazol	Streptomycin	Aureomycin	Chloromycetin	Terramycin	Bacitracin + Neomycin + Erythromycin
Staph. aureus								
Healthy subjects	33	2– 9	2– 9	0	0	0	0	0
Patients	161	37–155	32–136	9–40	1–3	3–15	1–3	0
Staph. albus								
Healthy subjects	403	13–112	5– 41	1– 9	2–19	0	2–19	0
Patients	279	37–228	23–133	8–41	7–36	7–42	7–36	0

Figures indicating resistant colonies give variations from the lowest to the highest number of resistant colonies (cf. text).

The material includes *staphylococci* isolated from cultures and from exposed agar plates.

amount possible of resistant colonies, i.e., one strain from each resistant test, and the highest number possible, i.e., all the colonies examined.

The number of *Staph. aurei* isolated from the wards supersedes by far the number isolated from the private rooms. From 4 to 41 colonies of *Staph. aurei* were isolated from each ward (a total of 50 *Staph. aurei* + *albi* were examined from each ward), but only 3 of the 10 private rooms disclosed the presence of *Staph. aurei;* 5, 9, and 19 colonies, respectively, were isolated from the 3 rooms (a total of 33 colonies). It proved impossible to isolate a single *Staph. aureus* strain among the 50 colonies from the remaining 7 private rooms.

Table 3 records that strains which are resistant to the various antibiotics and sulfa preparations are encountered in larger amounts in the wards than in the private rooms; 37-155 penicillin resistant *Staph. aurei* and 37-228 resistant *Staph. albi* were found in the wards as opposed to 2-9 and 13-112 from the private rooms.

The sulfa resistant *staphylococci* were also more abundant in the wards, viz., 32-126 *Staph. aurei* and 23-133 *Staph. albi* as opposed to the figures from the private rooms of 2-9 and 5-41, respectively.

Nine-40 streptomycin resistant *Staph. aurei* were isolated from the wards but not a single one from the private rooms. The corresponding figures for the *Staph. albi* were 8-41 and 1-9.

Results from the sensitivity tests with aureomycin and terramycin were all in accord; 1-3 *Staph. aurei* and 7-36 *Staph. albi* which were resistant to the two antibiotics were isolated from the wards. No *Staph. aurei* resistant to the above two antibiotics were isolated from the private rooms, but 2-19 resistant *Staph. albi* strains were found.

Three-15 chloromycetin resistant *Staph. aurei* and 7-42 resistant *Staph. albi* were isolated from the wards; all the *staphylococci* from the private rooms proved sensitive to chloromycetin.

All *staphylococci* from all 20 rooms were sensitive to bacitracin, neomycin, and erythromycin.

DISCUSSION

The material from De Gamles By shows beyond doubt that penicillin resistant *staphylococci* occur more frequently among the patients and hospital staff than among the

healthy old inhabitants of the institution. The percentage of resistant *staphylococci* isolated from patients and staff ranges among the highest published from other units.

Since the inhabitants primarily are admitted to the hospital it should be realized how much their chances are augmented of becoming carriers of penicillin resistant bacteria, partly because of their contacts with the hospital furniture, with other patients, and with the hospital staff, and partly because they aspire "hospital air." All inhabitants of the institution have been through the hospital before it is decided whether they are going to live in the institution proper or whether they should remain in the hospital. Hence, it cannot be denied that the figures from the "healthy department" fail to represent normal conditions as found among the general population. But although the freshly admitted patients are exposed to a certain hazard of becoming carriers of penicillin resistant *staphylococci* it must also be borne in mind that these *staphylococci* are not equally resistant to all other antibiotics.

Various methods might be suggested to restrain a dissemination of the resistant strains within the hospital area. The staff might apply gauze masks, but if the unintermittent care required by old people is considered, it would soon prove impracticable, at least for the nurses to change their coats for every visit to the patient. Even if an arrangement were made for less crowded wards, the old people would have a sensation of imprisonment if they were denied any intercommunication with their fellow patients. We can therefore only hope that the introduction of new antibiotics will keep pace with the occurrence of strains which are resistant to the already existing antibiotics.

SUMMARY

In De Gamles By 67 per cent of the patients, 52 per cent of the staff, but only 37 per cent of the healthy old inhabitants are carriers of nasal *Staph. aurei*. Penicillin resistant nasal *Staph. aurei* were found in 54 per cent of the patients, in 37 per cent of the staff, and in 12 per cent of the healthy subjects. Sulfa resistant nasal *Staph. aurei* were isolated from 25 per cent of the patients, from 15 per cent of the staff, but only from 7 per cent of the healthy subjects. A few of the isolated strains found in the patients were resistant to streptomycin, chloromycetin, aureomycin, and terramycin, but such strains were not encountered among the staff and the healthy subjects.

Nasal *Staph. albi* were found in 85-100 per cent of the persons examined. Penicillin resistant strains were more common in patients (62 per cent) and staff (74 per cent) than in the healthy subjects (19 per cent). Sulfa resistant *Staph. albi* were isolated from 23 per cent of the patients and from 30 per cent of the staff, but from only 9 per cent of the healthy subjects. Strains which were resistant to streptomycin, chloromycetin, aureomycin, and terramycin were also found more often in the patients and the staff than in the healthy subjects.

All the examined *Staph. aureus* and *Staph. albus* strains were sensitive to the three most recent antibiotics, bacitracin, neomycin, and erythromycin.

Staph. aurei were much more common in the air and on the furniture in the wards than in the rooms inhabited by healthy old people. Strains isolated from the wards were more resistant to penicillin and the sulfonamides than similar strains encountered in rooms inhabited by healthy old people.

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BOOK REVIEWS

THE JOSIAH MACY, JR. FOUNDATION 1930-1955. A Review of Activities, Josiah Macy, Jr. Foundation, New York, 1955, 174 pages.

It is fitting that special tribute should be paid to the activities of the Macy Foundation in the Journal of Gerontology. This Journal received support from the Foundation for 5 years until it grew strong enough to finance itself, and the Gerontological Society to which the Journal belongs was founded in 1945 as a direct outgrowth of the conference group on the problems of aging of the Foundation which was active from 1940 to 1953—a period much longer than that of any of the other 18 conference groups of the Foundation. Those of us who have seen the evolution of the organization and conduct of these conference groups realize their unique effectiveness. Their chief purpose is to bring about communication among scientists. They are not intended for the presentation of finished work in any field but to focus the attention of investigators in several specialties on problems encountered in investigations under way. Brief accounts are sufficient to explain them. The discussions, later printed in detail, show how surprisingly the problems can be clarified by this kind of multidisciplinary approach. It was good strategy on the part of the Foundation to activate the U.S. Public Health Service by the creation of a unit on gerontology within the division of physiology of the National Heart Institute. This unit was later discontinued but the interest of the government in problems of aging has grown immensely.

International communication among scientists has also been constructively advanced by the Macy Foundation. Witness the International Congress of Mental Health which, under the Presidency of Dr. Frank Fremont-Smith, Medical Director of the Macy Foundation, organized the World Federation of Mental Health in London in 1948. This World Federation has expanded rapidly and in 1954 had 86 member associations in 41 countries and several transnational associations. Likewise in our own field of gerontology the Macy Foundation has been internationally minded, helping to finance the travel of well chosen scientists to two international congresses, the second International Gerontological Congress in St. Louis in 1951 and the third one in London in 1954. The Macy Foundation in the United States and the Nuffield Foundation in England are pioneers in this field of gerontology. The objective is to make the whole life fruitful, not merely the period of youth, not alone in this country but everywhere. It is not by chance that the Macy Foundation assumed this leadership in the problems of aging both nationally and internationally. Credit is due to the vision of Dr. Ludwig Kast, the first president of the Foundation, who invited the National Research Council to make a survey of the problem of arteriosclerosis both at home and abroad which directed attention to the influence of aging on degenerative diseases of the blood vessels and on human welfare in its many aspects.

While the conferences of the Macy Foundation have proved of great value to many, have attracted wide attention, and have cost $827,397 in the period 1948-1954, direct grants for research have been made inconspicuously and wisely. The sum of $4,268,388 has been expended on 842 projects. The fields of stated special interest include *National Defense*, *Medical Education*, the *Health of the Community*, the *Whole Patient*, the *Life Cycle*, the *Individual and the Group*, and *Research in Medicine*. Aging is properly included in the *Life Cycle*.

The financial resources of the Foundation are not great as foundations go now-a-days. The present value of the endowment is stated as well in excess of 28 million. It would be difficult to find any organization with which it is more a pleasure to deal. One is not kept waiting for months to discover whether it is likely that an application will be acted on favorably.

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COST OF MEDICAL CARE FOR THE AGED, by George H. Houck, Oswald Nielson, and Calvin W. Churchill. Business Research Series No. 7, Graduate School of Business, Stanford University, California, 1955, 34 pages, paper bound.

This 34-page pamphlet, with inclusive title, actually is a report of findings at a single home for the aged, as explained in the subtitle: A Case Study Covering Experience in the Masonic Home At Decoto, California in 1952.

The Home cares for just over 300 residents, about 40 per cent male and 60 per cent female. Medical care includes treatment and prevention; visits by members of a group practice unit of physicians to residents in the Home; visits by residents of the Home to these physicians in their group practice clinic; care in a general hospital; dental treatment; services of an optometrist.

The total *direct* costs for medical care at the Home during a recent twelve month period were almost $69,000, or $229 for each resident. No indirect overhead costs are included in these figures. The largest items were salaries of nurses and other personnel in the infirmary of the Home (44.8%); contract fees for medical care (23.4%); hospitalization costs (12.6%); surgical supplies (7.4%); medicines (7.1%).

A number of tables are presented analyzing the costs of hospitalization, physician visits, and vital statistics of residents of the Home.

The arrangements for medical care at this Masonic Home are somewhat atypical because of the proximity of an outstanding medical group practice unit and a hospital at which its members serve. Most other homes for the aged would have to work out different programs and would wish to include such overhead costs as those incurred in maintaining an infirmary.

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EARNING OPPORTUNITIES FOR OLDER WORKERS, edited by Wilma Donahue, University of Michigan Press, Ann Arbor, 1955, 277 pages, $4.50.

Earning Opportunities for Older Workers is devoted to the problems of wage earners who, because of their age, find it difficult to continue in their jobs or find new jobs. It is based primarily upon papers presented at the University of Michigan's Sixth Annual Conference on Aging. The 35 authors contributing to this text have been drawn primarily from the ranks of industrial management, organized labor, the medical profession, and Federal, State, and local governments.

Workers in the field of gerontology who may have occasion to correct certain popular misconceptions, such as the alleged decline in work performance with advanced years or the pension and insurance costs involved in hiring older workers, will find authoritative information in this book. It also offers practical suggestions to employers and community organizations on how to put aged people to more productive use.

Secretary Oveta Culp Hobby introduces the topic by outlining the findings of the New York State Joint Legislative Committee concerning the roadblocks between the older worker and the job: the age barrier itself, compulsory retirement, unfair pension policies, inadequate research, lack of counseling, lack of sheltered workshops, little chance for home employment, and lack of organized promotional drives. Subsequent authors give details regarding these roadblocks and tell what is being done to remove them. The first half of the book contains a digest of recent research studies on the older worker and discusses the problem from various points of view. The latter half describes successful experiments in older worker utilization.

In the first section, Trends and Factors in the Employment of Older Workers, policies and practices of employers, unions, and government are presented. Three trade unionists—Pollack, Solenberger, and Hughes—consider the probable impact upon the economy if increasing numbers of older workers are excluded from productive roles and point out various steps taken by unions to prevent arbitrary age limits on employment. Representing management, John Convery stresses the importance of the older worker's responsibility to help himself. He cites the progress that has occurred in management acceptance of older workers. William C. Fitch of the Bureau of Old Age and Survivors' Insurance gives evidence to show that government insurance plans have not tended to discourage older people from working. The claim is sometimes made that an employer's pension and insurance costs are greater if older workers are hired. William Wandel of Farm Bureau Insurance Companies explains why this claim is untenable.

Robert C. Goodwin sets forth the two-fold principle of the Bureau of Employment Security's placement program. One is the scientific principle of individual differences and the other is the belief in the intrinsic worth of every individual. In line with this second objective he advocates a partisan attitude toward the older worker which would result in an unwillingness to accept apparent indications of declining capacities in old age without closer scrutiny. Taking Inventory of the Older Individual as a Worker attempts this scrutiny. Distinguishing between skill and work method, a psychologist shows how changes in work method operate to sustain efficient performance with advancing age. Dr. William Sawyer discusses how, through proper job placement, the health and physical well being of older workers can be maintained. Attitudes toward work are explained by Jack Weinberg, M.D. He mentions how changes in capacity and fear of retirement may lead to inefficient performance and how such fears may be overcome. Finally the strategic importance of counseling is brought out by Charles E. Odell of the Bureau of Employment Security, Division of Counseling and Placement. Since a large proportion of workers are obliged to change jobs after 40, they must face the necessity of planning a career for the later years. Studies have proved that twice as many older workers were placed, or found jobs on thir own, when exposed to intensive vocational counseling and placement services. He describes what is being done by the United States Employment Service and other agencies to provide counseling and training.

Older women workers face many of the employment barriers which trouble older men. In addition there are certain difficulties peculiar to older women. For example, the greater life expectancy of the average women intensifies the problem of pension costs. Another problem is that of the older housewife forced to go to work without having had recent work experience. These and other situations are discussed in a section, Older Women in the Labor Force. Contributors to this section include Pearl Ravner of the Women's Bureau, Marguerite Coleman of the New York State Division of Employment, and several employers of women.

In a section, Adapting Jobs to the Older Worker, examples are given of what is being done within specific enterprises to adapt jobs to the changing capacities and social circumstances of aged people. Creating New Earning Opportunities for Older Workers approaches the matter from the community organization standpoint and describes successful organized attempts to provide additional jobs for senior citizens.

The publication concludes in a philosophical mood as Martin Gumpert, M.D., draws an inspiring distinction between Making a Life and Making a Living.

There is an outstanding bibliography on the employment and earning opportunities aspects of aging in the back of the book that should be useful to research workers and others looking for reference materials.

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THE STATES AND THEIR OLDER CITIZENS, a study directed by Ernest W. Burgess and Sidney Spector, The Council of State Governments, Chicago, 1955, 176 pages, including 51 pages of appendix tables, $3.00.

This is a report prepared at the request of the Governors' Annual Conference to the Council of State Governments in 1954 that a study of the problems of aging be made and the findings presented at their 1955 meeting.

It begins with a statement of a ten-point "Bill of Objectives for Older People" covering work; income; living arrangements; physical and mental health; participation in community life, social services; research and professional training; and freedom, independence, and initiative. This is followed by a very brief statement of the principal problems and a fifteen-point suggested program for action. All of this is preliminary to the three main sections of the report: Origins, Magnitude and Nature of the Problem; Action in the States; and Coping with the Problem. All the material is presented with a background of numerous statistical tables, charts, and graphs.

About one-half of the states have already established legislative committees or governor's councils to study the problem and propose action. States have gone about the problem in various ways, some being ahead in certain aspects of the problems, others in other.

Part II discusses briefly selected projects and typical recommendations for action suggested by state study groups under each of the ten points of the Bill of Objectives: (1) equal opportunity for work; (2) maintaining an adequate income; (3) home living and family relations; (4) homelike institutional care; (5) physical health; (6) mental health and rehabilitation; (7) participation in community activities; (8) social services; (9) research and training; and (10) organization.

The pattern for the discussion of each of these is: first, a brief statement of the general problem; second, the situation, dealing quite largely with statistics; third, examples of state action; and fourth, typical recommendations that have been made by various state study groups.

This is one of the briefest and yet most comprehensive statement of the problems of the aging population. The many tables throughout the report and in the appendix present a wealth of information not easily available elsewhere.

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BOOKS RECEIVED

Books received since August 1, 1955, are acknowledged in the following list:

Cost of Medical Care for the Aged (A Case Study Covering Experience in the Masonic Home at Decoto, California, in 1952), by George H. Houck, Oswald Nielson, and Calvin W. Churchill, Business Research Series No. 7, Graduate School of Business, Stanford University, Stanford, California, 1955, 34 pages, paper bound (reviewed in this issue, page 90).

Fact Book on the Aged in New York City, Welfare and Health Council of New York City, 44 East 23 Street, New York 10, New York, 1955, 83 pages, mimeographed, paper bound, $1.00.

Josiah Macy, Jr. Foundation 1930-1955, a Review of Activities, Josiah Macy, Jr. Foundation, New York, 1955, 174 pages (reviewed in this issue, page 90).

Earning Opportunities for Older Workers, edited by Wilma Donahue, University of Michigan Press, Ann Arbor, 1955, 277 pages, $4.50 (reviewed in this issue, page 91).

Life Will Begin at 100, by Raymond J. Jeffreys, Capitol College Press, Columbus, Ohio, 1955, 239 pages $3.75.

States and Their Older Citizens, a Study directed by Ernest W. Burgess and Sidney Spector, the Council of State Governments, Chicago, 1955, 176 pages, $3.00 (reviewed in this issue, page 91).

Suggested Standards and Practices for Organizing and Operating Activity Programs for Older Adults, by the Committee on Leisure Time Activities of the Division of Services for the Aging, Nassau County Council of Social Agencies, 14 pages, multilithed, paper bound, 35 cents in coins to: Mrs. George Heitler, 568 Rockville Court, Oceanside, Long Island, New York.

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Section C

Index to Current Periodical Literature

INDEX TO CURRENT PERIODICAL LITERATURE

NATHAN W. SHOCK

Gerontology Section
National Heart Institute
National Institutes of Health

The subject categories are those in *A Classified Bibliography of Gerontology and Geriatrics* by Nathan W. Shock published by Stanford University Press, Stanford, California (1951). Only major headings are used and the Roman numerals correspond to those given in the bibliography. In so far as possible, references are classified according to organ systems. Thus most of the material on Geriatrics will be found under the organ system involved in the disease. Cross references are indicated by number at the end of each section. When available, abstract references are given *(B.A.—Biological Abstracts: P.A.—Psychological Abstracts: and P.I.—Population Index).* Abbreviations for journals are those used in *A World List of Scientific Periodicals Published in the years 1900-1933,* 2nd Edition. For journals not listed, abbreviations were devised according to the general rules used in the above source. It is impossible to cover all journals and list all papers concerned with aging and the aged. Authors and publishers are requested to call attention to publications or to send reprints to the Gerontology Section, Baltimore City Hospitals, Baltimore 24, Maryland. The assistance of the Forest Park Foundation, Peoria, Illinois, in the preparation of these materials is gratefully acknowledged.

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See also Nos. 15931, 15968, 16213.

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Figures 1 and 2 were intended by the authors to be reproduced in color, since they showed the presence of Weigert staining material. They have, however, been reproduced as black and white "negatives" on which the dark staining regions appear white. The captions for these two figures also describe the different color shades which could be observed in the originals.

Figures 2 and 3 were intended to be directly comparable, one taken in ordinary light and the other in polarized light. They were arranged so that they could be superimposed; however, figure 3 has been turned so that the left side is now on the right side. They, therefore, now form mirror images.